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New routes to biologically interesting heterocycles by palladium-catalyzed reactions

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To my joys

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THESIS AIM

Over the last few years, industry focused its efforts on the development of new technologies for pollution prevention.[1] This approach is the way of modern business. It uses less energy, requires minimal product separations, generally involves less capital investment and there is no impact on the environment. To move in this direction, scientists must bring themselves about these changes in a way that addresses the concern of Count Antoine de SaintExupery, author of "The Little Prince", who said: " *We have not inherited the land of our ancestors; we are borrowing the land of our children"*.

In the last years, green chemistry has been recognized as a a new approach to scientifically based environmental protection. Green chemistry "is the design of chemical products and processes which reduce or eliminate the use and the generation of hazardous substances in the design, manufacture and application of chemical products".[2] It utilizes a set of twelve principles[3] (Table 1) and the catalysis has a fundamental role.[4]

In the last decades, palladium-catalyzed reactions have become an important and extremely flexible tool for practicing organic chemists. [6,7] As palladium chemistry is generally tolerant of a wide range of functionalities, it is applicable to complex molecules. Thus, a large number of fine chemicals and biologically active ingredients have been prepared in fewer steps and with less wastes than classical methods. Even the design of heterocyclic synthesis has been deeply influenced and modified by the growing utilization of palladium catalysis,[8,9] as testified by the wide amount of studies on the palladium-catalyzed synthesis and functionalization of heterocycles.

In this context, during my doctorate activity, we investigated the construction of heterocyclic rings and the production of derivatives of heterocyclic compounds of biological interest through palladium-catalyzed reactions. In some cases, these synthesis have been performed in environmentally friendly solvents and organic compounds present in agroindustrial wastes have been used as starting materials to achieve their "chemical valorization".

Then, using our background on the Heck reaction it appeared to us particularly interesting to investigate the possibility to develop domino vinylic substitution/cyclization processes to obtain functionalised coumarins and 2-quinolones in molten salts, new reaction media having

interesting green properties (no detectable vapour pressure, possible recycling, thermal robustness).

Table 1. The 12 Principles of Green Chemistry.

1.	It is better to prevent waste than to treat or clean up waste after it is formed
2.	Synthetic methods should be designed to maximize the incorporation of all materials used into the final product.
3.	Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4.	Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5.	The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and, innocuous when used
6.	Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure
7.	A raw material of feedstock should be renewable rather than depleting wherever technically and economically practicable
8.	Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible.
9.	Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10.	Chemical products should be designed to preserve efficacy of function while reducing toxicity.
11.	Analytical methodologies need to be developed to allow for real-time, in-process monitoring and control prior to the formation *of* hazardous substances.
12.	Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions and fires.

At the same time, we explored in more detail the Heck reaction of β,β-diarylacrylamides and the results obtained prompted us to investigate the utilization of this chemistry for the preparation of 2-quinolone derivatives through an intramolecular carbon-nitrogen bond forming step. Concerning the cyclization step, the economic attractiveness of copper-based methods and the growing interest in copper-catalyzed syntheses[10] stimulated us to develop a copper-catalyzed protocol.

As part of our studies devoted to the construction of the benzo[*b*]furan skeleton via palladium-catalyzed cyclization of acetylenic precursors,[11] we explored the extension of our alkyne

chemistry to the preparation of lipophilic benzo[*b*]furan derivatives from cardanol, a natural renewable phenolic lipid obtained by vacuum distillation of the by-product of the cashew tree (*Anacardium occidentale L.)* industry.[12]

Finally, using catechins and epicatechins as substrates, organic resource obtained from wastes of wine industrial production, we investigated the utilization of the Suzuki reaction to obtain the corresponding arylated catechin derivatives.[13]

In all the synthetic protocols developed in this work we have taken advantage of several green chemistry principles. In fact, using palladium-catalysis it has been possible to maximize the incorporation of atoms and realize one-pot or domino processes. Raw material of feedstock and alternative no-toxic solvents have been used.

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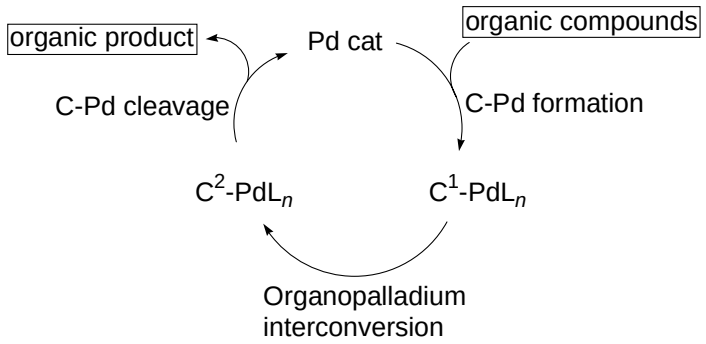
BACKGROUND OF PALLADIUM-CATALYZED REACTIONS

Over the last three-four decades palladium has definitely influenced and improved organic synthesis.[1] Being the 46th atom in the periodic table, Pd is a second row transition metal of moderately large atomic size, larger than Ni but smaller than Pt. Its size influence significantly its chemical properties, such as the moderate stability of its compounds and their versatility and selectivity. Palladium typically exists in the 0 and +2 oxidation states (separated by a relatively narrow energy gap), rarely +1, +2, +4; thanks to these characteristics one-electron or radical processes are relatively rare whereas two electron oxidation and reduction is ready and reversible. Pd 's electronic configuration is [Kr]4d^{10} and tends to form d^{10} Pd(0) and d^{8} Pd(II) complexes of relatively low oxidation states, it is consequent that Pd is rather *soft* than the smaller Ni and the larger Pt. Coupled with the ready formation of coordinatively unsaturated species of 16 or even less electrons providing one or more empty coordination sites, Pd can indeed provide simultaneously at least one each of empty and filled nonbonding orbitals. Thus it can be understood why Pd can readily participate to concerted reactions with low activation energies. Some of the selectivity features, stereoselectivity is one of these, can be readily attributed this characteristic. The most significant consequence of its high propensity to run in concerted reactions, is the high affinity for nonpolar π-compounds, such as alkynes, alkenes and even arenes. Furthermore, it can also readily form σ bonds with nonbonding electron donors, such as amines, imines, nitriles, phosphines, phosphites, and various other N, P, S, O containing donors. Carbon monoxide and isonitriles are also representative examples of *C*-centered *n*-electron donors. Thank to this, Pd-mediated reactions are usually carried up in mild conditions. Palladium is relatively unreactive toward many functionalities, such as aldehydes, ketones, esters, amides, as well as nitro and ciano groups permitting to have often a wide generalization of the procedures. In the majority of Pd-catalysed reactions, some interconversions between Pd(0) and Pd(II) species must occur. As stated earlier the interconversion Pd(0) over Pd (II) is kinetically easily occurring in either direction under one set of reaction conditions so it is possible to have catalysis. Thus, this easy interconversion appears to be serving as a very favourable factor rather than a limitation. Finally, palladium appears to be relatively no-toxic, though very few substances can be definitely considered no-toxic at all.

1.1 Pd-Catalyzed reactions

Synthesis of organic compounds *via* organopalladium complexes in most cases involves generation of C-Pd bonds and their subsequent cleavage (Scheme 1).



Scheme 1

Pd catalysts and Pd-containing intermediates in a catalytic cycle itself must be regenerated in the reaction vessel under one set of reaction conditions without any additional external manipulations. This requires that the sum of ΔFOS (i.e., change in formal oxidation state) for the whole catalytic cycle must be zero. This is but one of many "zero sum" principles governing various aspects of chemical processes.

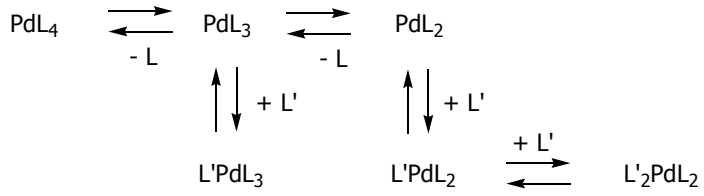
There are different kinds of reagents and reactions that can reduce Pd(II) to Pd(0) species or provide the reverse oxidation. Pd(II) species added as precatalysts might be transformed into catalysts that appear in catalytic cycles themselves. A wide variety of reactions involving the reactants, ligands, and/or solvents present in a given reaction mixture can reduce Pd(II) species. Therefore, in some cases Pd(II) reduction can be achieved without adding externally reducing agents but by internal reduction. In fact it's known that reductive elimination, reductive decomplexation, and some processes involving nucleophilic attack on ligands can reduce Pd(II) species. Although the majority of Pd-catalyzed reactions are initiated by Pd(0) catalysts (which then undergo a series of Pd(0)-Pd(II) redox processes) there are many other Pd catalyzed reactions that are initiated by Pd(II) complexes. Most of the Pd(II) initiated reactions do involve reduction of Pd(II) species to Pd(0) species. In many of these reactions,

the Pd(0) species must be externally oxidized to regenerate the original Pd(II) catalysts. For this purpose in addition to O_2, and CuCl, quinones (e.g., DDQ), peroxides (e.g., t-BuOOH) halogens, and halo-derivatives including organic halides have been used.

1.2 Organo-Palladium complexes

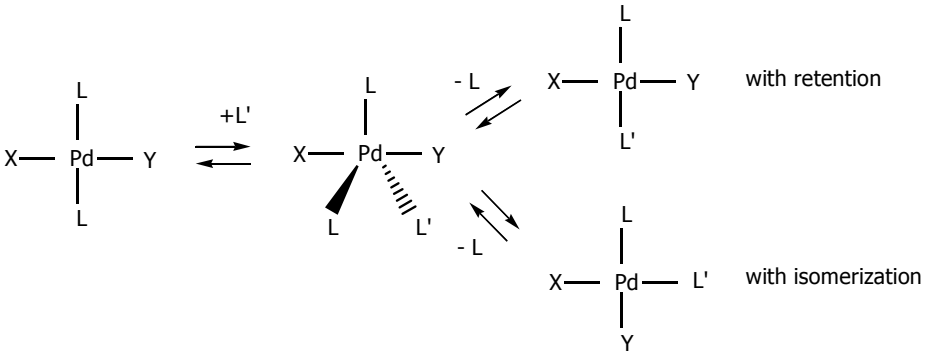
Pd(0) complexes tend to exists as coordinatively saturated 18-electron tetrahedral d^{10} complexes, but they can readily dissociate into coordinatively unsaturated 16 or less-electron d^{10} species. On the other hand, Pd(II) complexes tend to exist as coordinatively unsatured 16-electron square planar d^8 complexes. Although they are reluctant to form coordinatively saturated 18 electron five-coordinated d^8 complexes, such complexes are kinetically readily accessible, and they can serve as transient intermediates in ligand substitution. Pd(II) d^8 complexes may also undergo substitution by dissociative processes, which must involve 14 or less-electron species as transient intermediate. In all of these processes, the crucial requirement is the coordinative unsaturation or the presence of one or more valence-shell empty orbitals as Lewis acidic sites (Scheme 2).

Dissociative ligand substitution reactions of 18-electron d^{10} Pd(0) complexes

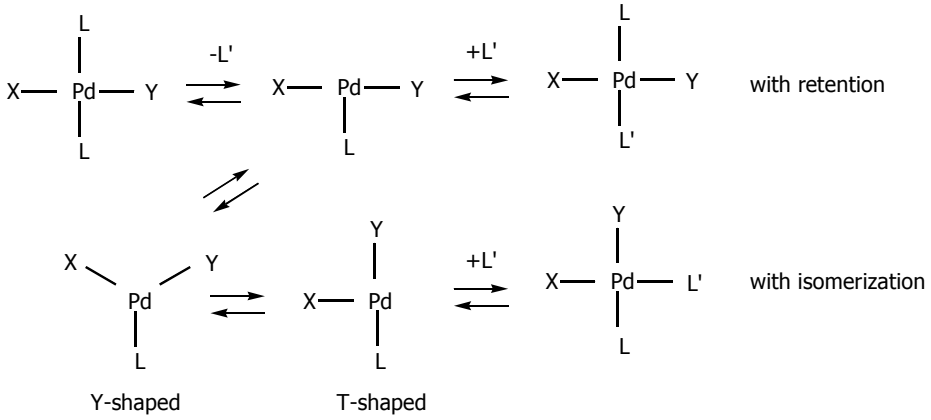


Scheme 2

Associative ligand substitution reactions of 16-electron d^8 Pd(II) complexes



Dissociative ligand substitution reactions of 16-electron d^8 Pd(II) complexes

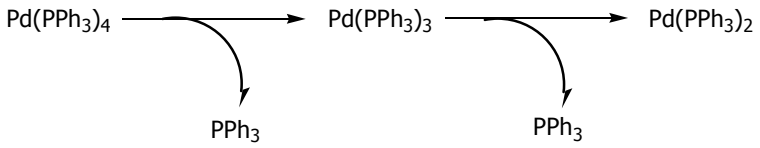


Scheme 2

1.3 Ligands for Organo-Palladium complexes

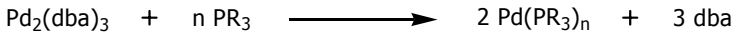
The nature of the ligand to be incorporated, especially its nucleophilicity or basicity, the electrophilicity or acidity of the leaving ligands and the nature and stereochemistry of the other ligands are factors that affect the rate and equilibrium of the ligand substitution. Two of the most commonly used palladium(0) complexes are the commercially available $Pd(PPh_3)_4$, unstable in air and light sensitive, and $Pd_2(dba)_3$ (dba = dibenzylideneacetone), whose storage and manipulation is quite easier than the former one. When $Pd(PPh_3)_4$ is used, the coordinatively unsaturated, catalytically active $Pd(PPh_3)_2$ (14 electrons species) is generated

via a two-step equilibrium process involving the initial loss of a phosphine ligand to give $Pd(PPh_3)_3$ followed by the loss of a second phosphine ligand (Scheme 3).



Scheme 3

In the $Pd_2(dba)_3$ complex each palladium is coordinated to three olefinic double bonds. Being dba a weaker ligand than phosphine, $Pd_2(dba)_3$ represents a useful a source of Pd(0) to prepare palladium-phosphine complexes *in situ* by a ligand exchange reaction with a variety of monodentate and bidentate phosphines (Scheme 4). This quite easy exchange is particularly useful when the reaction requires the use of Pd(0) complexes for instance containing chiral or electron-rich bulky phosphines.



Scheme 4

Palladium on charcoal, or other supported palladium metal catalysts, can also be used as a source of Pd(0). In these cases, reactions occur under heterogeneous conditions; the presence of phosphine ligands may involve soluble palladium complexes in a sort of a like $Pd(PR_3)_n$ catalyst system. [2] Palladium(0) species are frequently formed *in situ* through the reduction of palladium(II) species by several reagents such as alkenes, terminal alkynes, carbon monoxide, alcohols, amines, formate anions, metal hydrides, butyl lithium as well as phosphines. [3]

The most commonly used palladium(II) salts are commercially available $PdCl_2$ and $Pd(OAc)_2$, very often utilized as phosphines complexes such as $PdCl_2(PPh_3)_2$, $Pd(OAc)_2(PPh_3)_2$, tipically formed *in situ* combining $PdCl_2$ or $Pd(OAc)_2$ with PPh_3. Palladium(II) salts are fairly electrophilic species and tend to react with electron-rich compounds such as alkenes and alkynes, as well as arenes. Typical reaction of palladium(II) salts with alkenes or alkynes afford π-complexes.[see

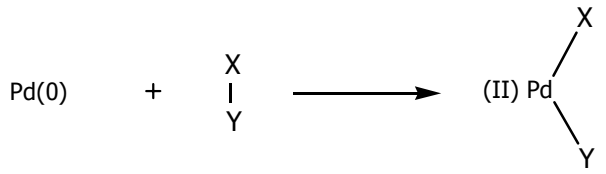
section 1.5] Palladium(0) complexes have usually nucleophilic character. Most of the catalytic processes based on their utilisation involve, in the initial step, their reaction with a variety of covalent polar and non polar single bonds such as H-H, N-H, O-H, C-H, C-O, as well as C-halogen; the latter is most employed. With arenes, palladium(II) salts such as $Pd(OAc)_2$, can produce palladation intermediates, basically through an electrophilic substitution reaction. These palladation intermediates can give rise to homocoupling reactions, [4] acetoxylation reactions, [5] or, in the presence of alkenes, vinylic substitution reactions. [6] In many Pd(II)-catalyzed reactions, Pd(II) species are reduced to Pd(0) species at the end of each cycle. Hence, the presence of oxidants such as Cu(II) salts and MnO_2 are required to make the reaction catalytic with respect to Pd(II).

1.4 General patterns of Pd and Pd complexes chemical processes

There are many different processes to generate palladium intermediates from Pd(0) and Pd(II). In this section some of most important patterns occurring in chemical processes involving palladium will be discussed, namely oxidative addition, insertion reaction, transmetallation, reductive elimination and electrophilic palladation.

1.4.1 Oxidative addition

The oxidative addition is the addition of an X-Y bond to Pd(0) [7] (Scheme 5) with cleavage of the covalent bond and formation of two new bonds. Since the two previously non bonding electrons of Pd are involved in bonding, the Pd increases its formal addition state by two units.[8]



X,Y = Atoms and groups containing H, C, heteroatoms and metals.

Scheme 5

The oxidative addition occurs with unsaturated complexes and leads to the formation of σ-organo-palladium complexes, containing an electrophilic palladium which, depending on reaction conditions, can undergo a variety of transformations. The substitution pattern of the arene plays an important role, since electron-withdrawing groups facilitate the oxidative addition, while electron-donating groups make difficult this process. Typically, oxidative addition is favoured by increasing the electron density on palladium, being the usual observed rate of oxidative addition with Csp^2-halogen bonds as follows: C-I > C-Br > C-CI > C-F (with aryl fluorides being almost inert). Vinyl triflates undergo facile oxidative addition while the reactivity of aryl triflates is more or less close to aryl bromides. Diazonium salts, aryl iodides, triflates and electron-deficient aryl-bromides do not generally requires ligands to go oxidative addition but are more disposed to undergo protonolysis and biaryl[9] formation during the reaction. Recently with the discovery of new electron rich ligands such us $P(t\text{-}Bu)_3$ or N-heterocyclic carbene ligands and Buchwald-type phosphines a some palladium-catalyzed reactions of aryl chlorides and alkyl halides are emerging. The cost and ready avaibility of aryl chlorides make them the most attractive aryl donator albeit they are the most sluggish precursors. Thus, efficient catalysis requires high temperatures in combination with highly basic and air-sensitive phosphines as ligands to allow oxidative addition. Recently, the development of a procedure using air-stable tri-t-butyl phosphonium tetrafluoroborate[10] has simplified the implementation of the sluggish aryl chlorides, especially in Heck type reactions. In general, oxidative addition is favoured by σ-donor ligands coordinated to the palladium center. Hence, though there are examples of reactions carried out under "ligand-free" conditions, ligands (and other coordinating additives), are frequently required not only to generate soluble palladium catalysts, but to influence the course of a reaction as well. The ligands can bear one or two sites of coordination, being named respectively, mono- or bidentate. In the presence of monodentate ligands (Figure 1), the initially formed cis-complex subsequently isomerizes to the thermodynamically stable trans-complex. Typically with bidentate ligands (Figure 2) the isomerization is rather difficult being the cis-complex the usual intermediate, even if Buchwald et al. [11] has recently shown that Xantphos [9,9-dimethyl-4,6-bis(diphenylphosphino)xanthene], [12] a rigid bidentate ligand with a wide natural bite angle, [13] can be trans-chelating in palladium complexes.

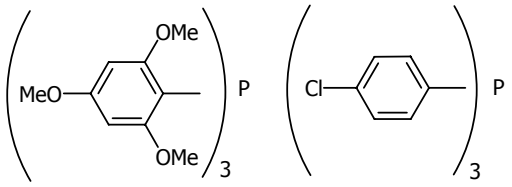
PPh_3

Most common ligand

$P(t\text{-}Bu)_3$; $P(cyclohexyl)_3$

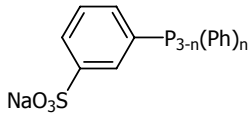
Phosphines that improve Oxidative Addition

ttmpp **tcpp**



Electron withdrawing and electron donating phosphines

Sulphonic Phosphines



Water soluble phosphines

Figure 1

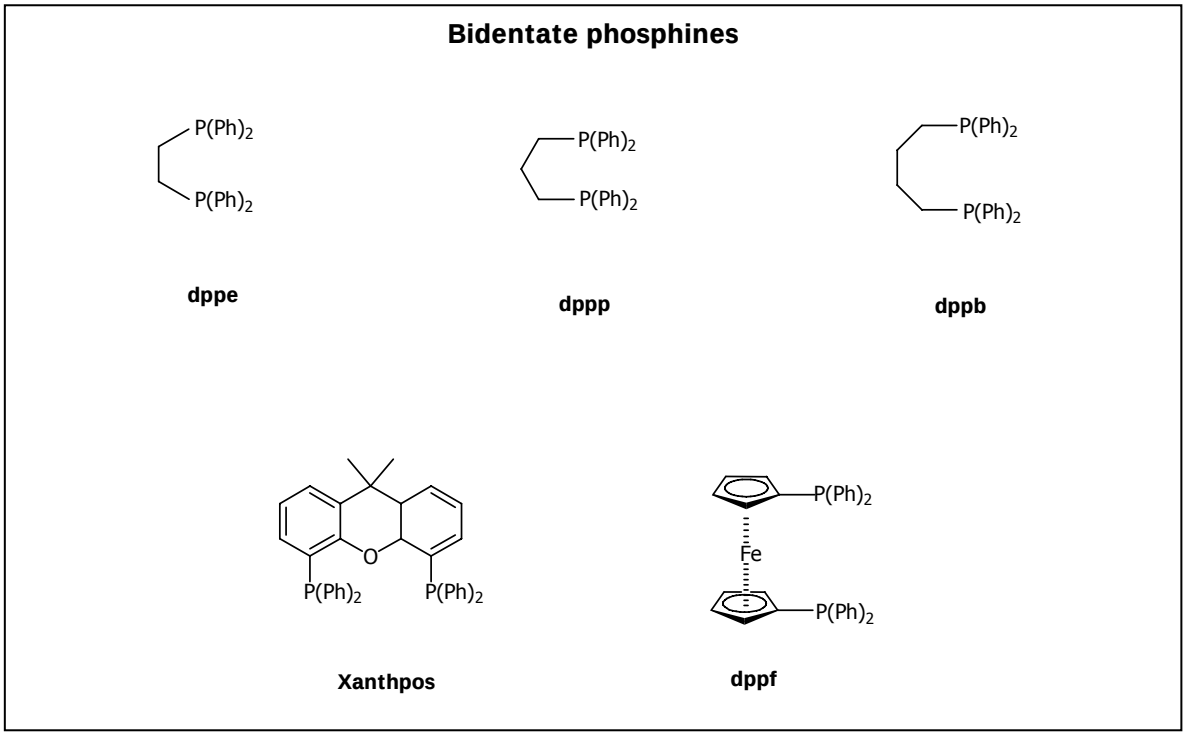


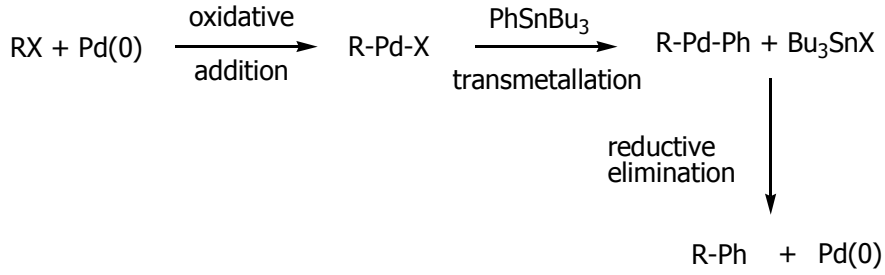
Figure 2

The use of additives such as halides, [14] can also play a significant role in controlling the reaction outcome of Pd(0)-catalysed reactions. Beneficial effects of such additives have been demonstrated and described throughout a huge number of papers. For example, Jeffery [15] has showed that the Heck could be run under mild conditions in the presence of $Pd(OAc)_2$, carbonate or bicarbonate bases and $^{n}Bu_4NCl$ as additive. Furthermore, the studies of Amatore and Jutand have shown that chloride anions can stabilize Pd(0) species providing more efficient catalytic cycles. [16] The nature of the halide anions is believed to influence the stability of five-coordinate palladium complexes[17] and the stability of dimeric palladium complexes in amination reaction. [18] The large ammonium cation plays also a significant role, since it can stabilize halide ligated zerovalent or divalent palladium-centered complexes. In some cases, a mixture of

ammonium salts can be used both as additives and solvents. [19] Even if $^{n}Bu_4NCl$ is generally superior to LICI in this respect, there are some cases in which the presence of LiCl has been found to provide rather more beneficial effects on Pd(0)-catalyzed reactions. For example LiCl has been shown to play a key role in the Stille reaction, [20] or in preventing homocoupling reactions of aryl iodides. [21] Hence, one can't exactly know *a priori* the course of a reaction since the general behaviour of phosphine ligands and additives is not always clearly understood. Furthermore, it may also significantly vary not only from one type of reaction to another, but sometimes in the same reaction; for example, switching from electron-rich to electron-poor aryl halides. [22] This lack of general theories can be due to the involvement of several consecutive steps in the catalytic cycle. Consequently, a given species can exhibit opposing effects on different steps of a catalytic cycle and on the reactivity of each intermediate depending on reaction conditions. Thus, in some case the conditions for a given reaction can involve several different procedures specific for specific substrates.

1.4.2 Transmetallation and reductive elimination

Transmetallation reaction occur between σ-organo-palladium complexes and organometallic compounds with Li, Mg, Zn, Zr, B, Al, Sn, Si, Ge, Hg, Tl, Cu, Ni and more other. The physical driving force of transmetallation is the generation of less polar bonds. The transfer of the organic ligand to a more electronegative metal is always favoured from a thermodynamic standpoint. The process proceeds smoothly, typically at room temperature.

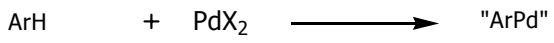


Scheme 6

As shown in Scheme 6 the reductive elimination step involves the cleavage of C-Pd bonds, the formation of a new C-C bond, and the reduction of Pd(II) to Pd(0).

1.4.3 Electrophilic palladation

The reaction of Pd(II) species with unfunctionalised arenes can afford aryl metal intermediates (Scheme 7). [23]



Scheme 7

If a functionalised arene is subjected to such a transfornation, *ortho-meta-* or *para*-palladation is usually observed.[24] Nevertheless, this procedure seems attractive in terms of atom economy, since catalytic amounts of the transition metal are required when an effective palladium(0) reoxidation system is used and no organic salts are produced.

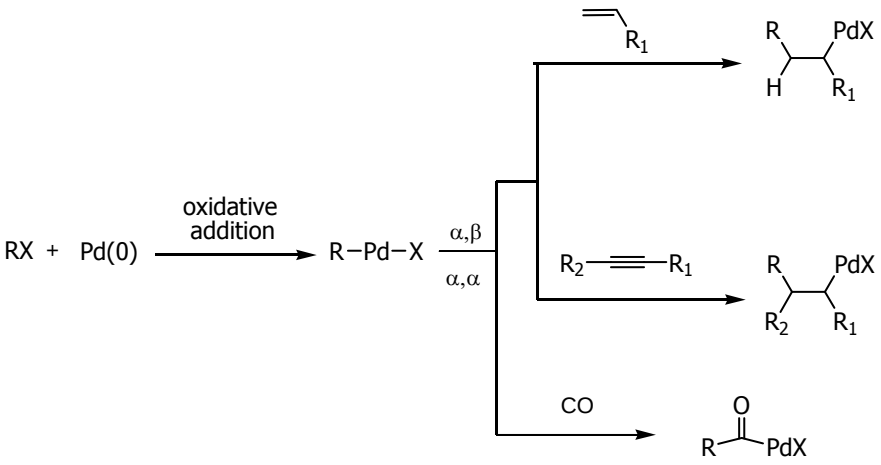
1.5 Reactivity of Organo-Palladium complexes

As stated earlier synthesis of any organic compounds via organopalladium complexes involve the interconversion of organopalladium intermediates, *i.e.* the generation and cleavage of C-Pd bonds.

Generally, palladium catalysis involves the intermediacy of σ- and π-complexes. Three types of π -complexes exist: η^2 type with alkenes and alkynes and η^3 with allyl compounds.

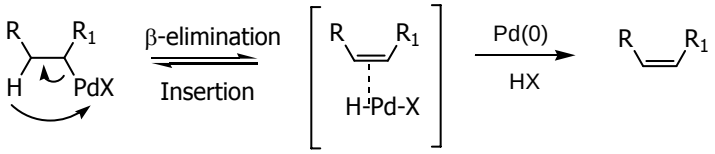
1.5.1 σ-Organo-Palladium complexes

Unsatured compounds react with σ-organopalladium complexes to undergo insertion reaction. Olefins and alkynes give rise to an α,β (or 1,2) type insertion and carbon monoxide, isonitriles, and carbenes to an α,α (or 1,1) type insertion (Scheme 8).



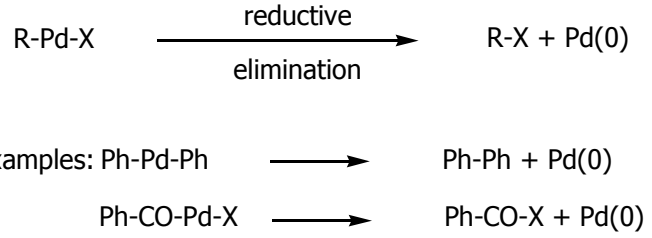
Scheme 8

These insertion intermediates react according to a variety of reaction pathways. In the presence of β-hydrogens, a *syn*-β-elimination of HPdX species can occur with the formation of a vinylic substitution product (Scheme 9). [25]



Scheme 9

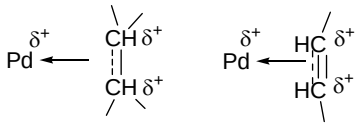
In the absence of β-hydrogens, a reductive elimination reaction can occur which affords a coupling derivative regenerating Pd(0) (Scheme 10).



Scheme 10

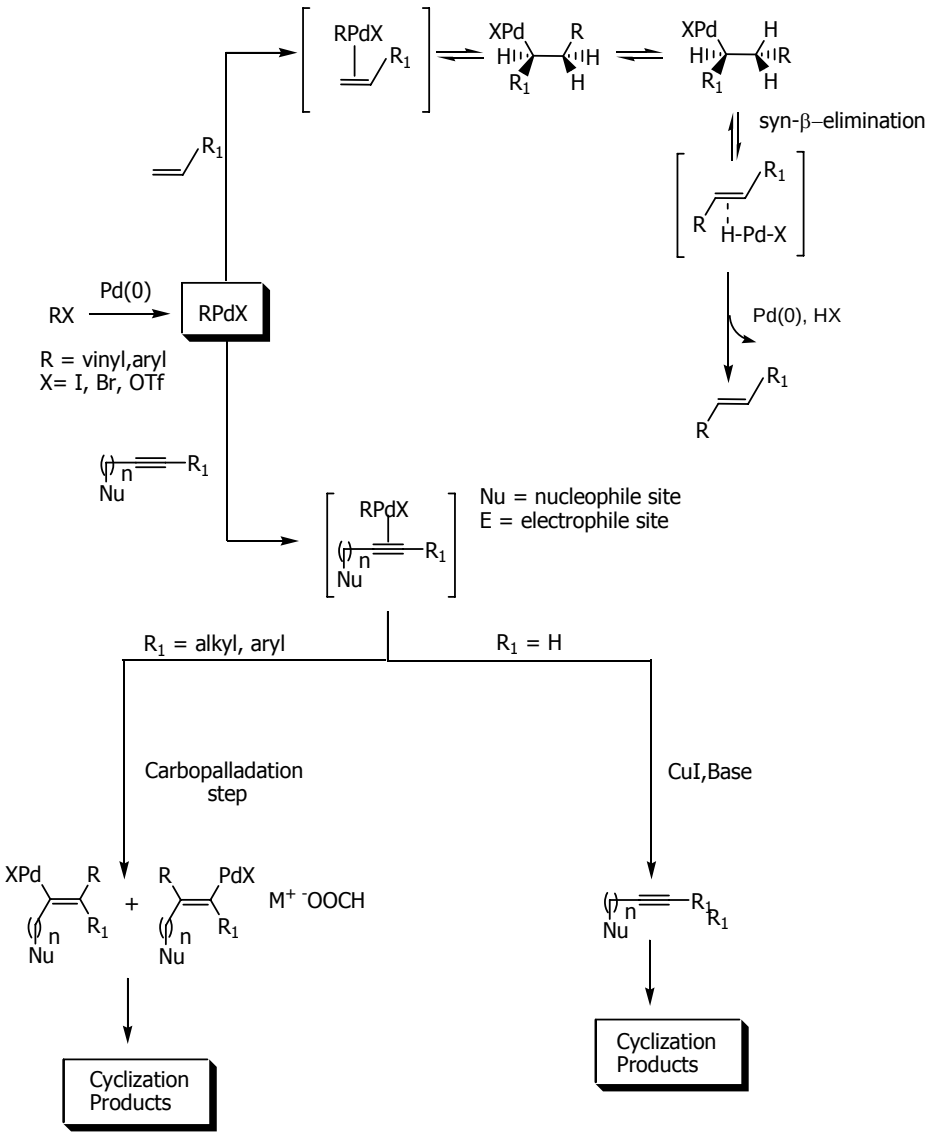
1.5.2 η^2-Organo-Palladium complexes

When Pd(II) salts or σ-organo-palladium complexes coordinate unsatured carcbon-carbon bonds like alkenes, alkynes, dienes, π -palladium - complexes are generate.



Scheme 11

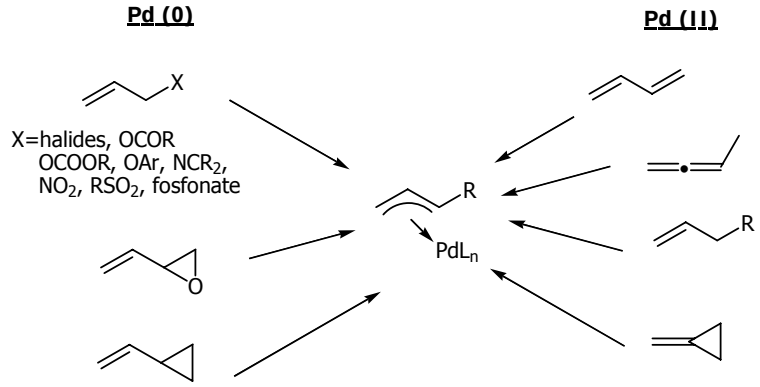
As shown in Scheme 11, both the acetylenic and the olefinic systems undergo a distortion of their structure because of the diminished order of bond due to the coordination. The effect can dramatically change depending on the type of substituents at the insature bond. Once formed, because of their decreased electron density at the carbon-carbon multiple bond, the complexes can undergo an intermolecular or intramolecular nucleophilic attack across the coordinated olefinic or acetylenic moiety. Intramolecular nucleophilic attack on π-palladium complexes by a heteroatom close to the carbon-carbon multiple bond is particularly useful and represent a powerful tool for an easy access to functionalized heterocycles. The reactivity of these complexes toward alkynes and alkenes will be discussed in the following section and is summarised in Scheme 12.


RPdX
XPd
R
H
R1
syn-β–elimination
H-Pd-X
Pd(0)
RX
RPdX
R = vinyl,aryl
X= I, Br, OTf
Pd(0), HX
Nu
Nu = nucleophile site
E = electrophile site
R1 = alkyl, aryl
R1 = H
Carbopalladation
step
CuI,Base
PdX
M+ -OOCH
Cyclization
Products
Cyclization
Products

Scheme 12

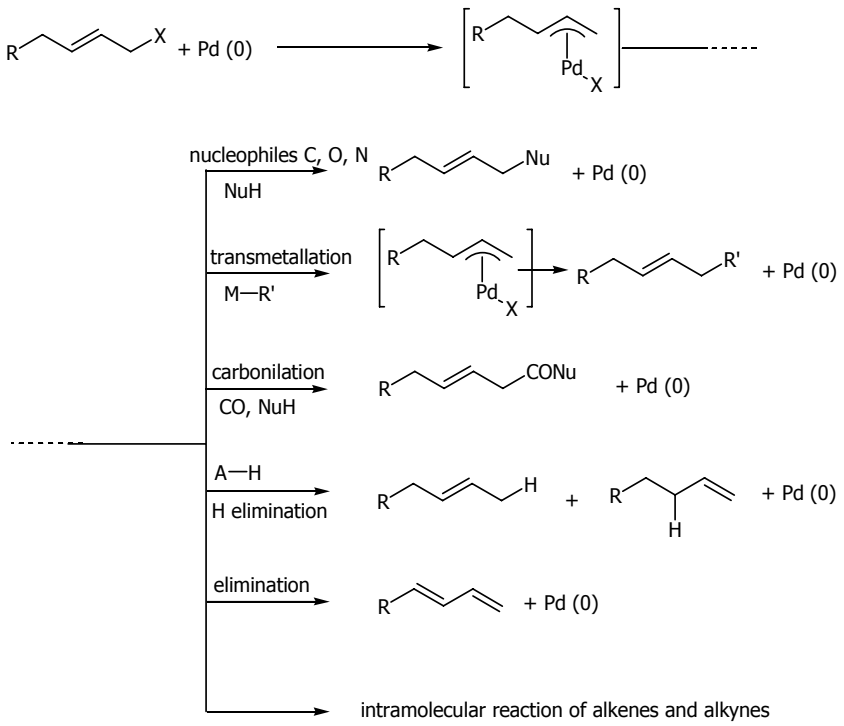
1.5.3 η^3-Organo-Palladium complexes

There are two different ways to generate the π-allyl palladium(II) complexes: by oxidative addition of allyl-derivatives such as acetate carbonate, nitro-compounds etc to Pd(0) or by reaction of different olefinic systems with Pd(II) salts in alkaline solution.(scheme 13). [26]



scheme 13

The reactivity of π-allyl palladium(II) complexes is showed in scheme 14. When π-allyl palladium(II) complexes is generated using Pd(II) salts , the last have to be added in stechiometric amount. In all the reaction of the following scheme Pd(0) is restored at the end of the catalytic cycle.


R
X
+ Pd (0)
R
Pd
X
nucleophiles C, O, N
NuH
R
Nu
+ Pd (0)
transmetallation
M—R'
R
Pd
X
R
R'
+ Pd (0)
carbonilation
CO, NuH
R
CONu
+ Pd (0)
A—H
H elimination
R
H
+
R
H
+ Pd (0)
elimination
R
+ Pd (0)
intramolecular reaction of alkenes and alkynes

Scheme 14

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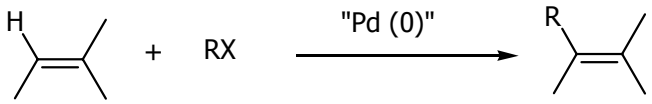
2. COMPLEX MOLECULES BY HECK, SONOGASHIRA AND SUZUKI-MYAURA REACTIONS

In 1960s Mizoroki[1] and Heck[2] independently discovered the palladium-catalyzed arylation and vinylation of olefins. It was demonstrated by Heck that arylpalladium salts, prepared by trans-metallation of organomercury compounds, constitute useful reactants in various vinylic substitution reactions. Independently, Moritani, Fujiwara, and colleagues conducted similar vinylic substitutions, but generated the organopalladium intermediates by direct electrophilic palladation of arenes. In these reactions the Pd(II) salt employed is reduced to Pd(0). A major improvement from a preparative point of view was demonstrated by Mizoroki, Heck and colleagues, who independently found that organic halides were suitable organopalladium precursors, and that the vinylic substitution reaction could be accomplished with a catalytic amount of palladium and a base, in the absence of a reoxidant (Scheme 1). This reaction was developed further by Heck and co-workers and was later referred to as the Heck reaction or Heck olefination .[3]



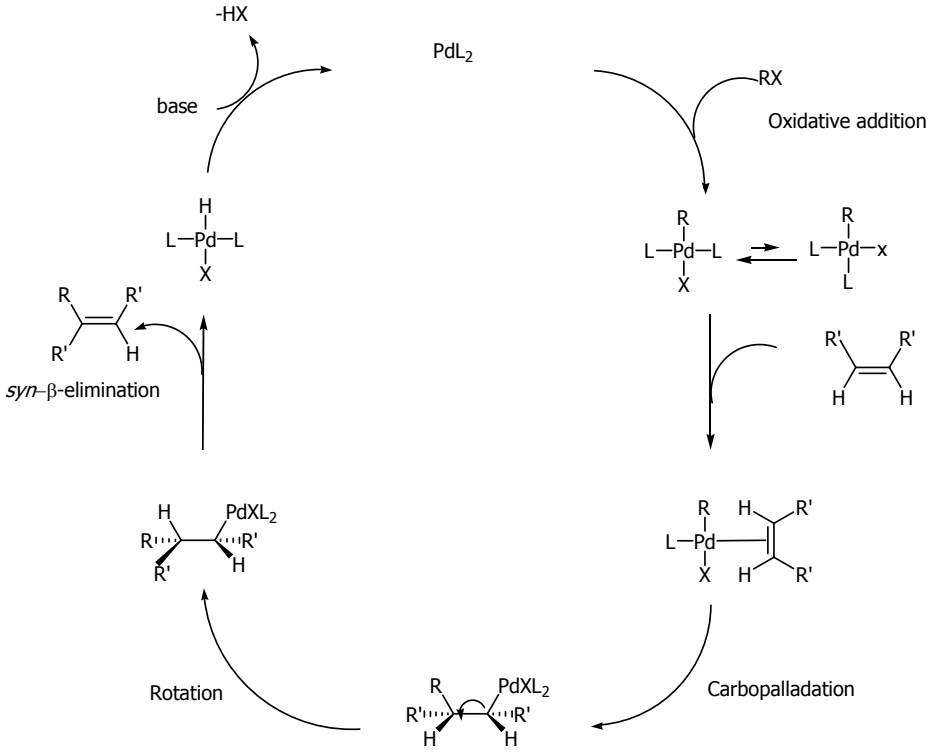
R = aryl, vinyl; X = I, Br, COCI, OTf, etc.

Scheme 1

Successively, several coupling reactions mechanistically related to the Heck reaction, as Sonogashira and Suzuki reactions, were developed. Thanks to this kind of reaction now is possible to perform the synthesis of complex molecules as polymer, heterocyclic compounds etc. rather easily. Subsequently, the general features of Heck and Suzuki reaction and a description of benz[*b*]furan core construction by Sonogashira coupling, are reported.

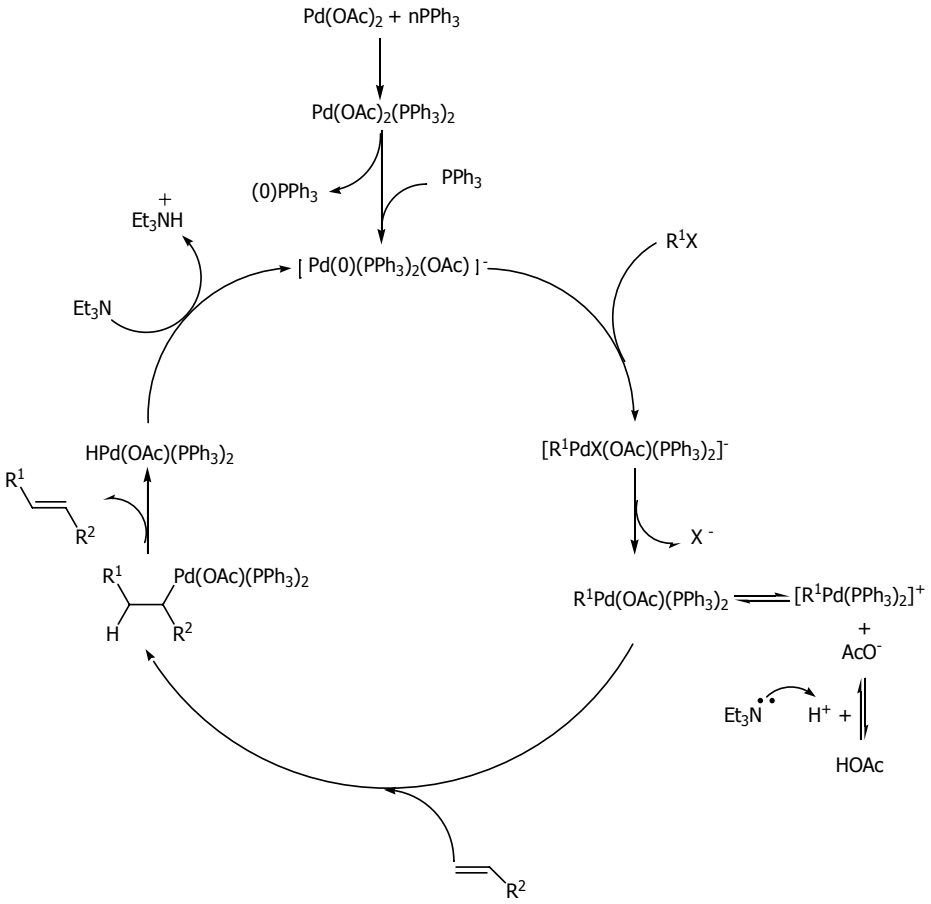
2.1 Heck reaction

Studies concerning mechanism of Heck reaction have been mainly performed on carbopalladation step[4] by computational chemistry. In Scheme 2 is reported the general mechanism of Heck reaction. The catalytically active species is a 14-electron complex, PdL_2[5], it is commonly generated in situ either from a palladium(0) complex or by reduction of relatively inexpensive palladium(II) acetate or chloride[6]. The first step of mechanism is oxidative addition of RX to the palladium(0) complex to generate a σ-alkenyl or σ-aryl-palladium(II) complex *cis*-$RPdXL_2$. Except for aryl iodides, the presence of ligands is necessary in order to effect at a reasonable temperature and ligands for Heck reaction are monodentate[7] and bidentate phosphines[8] and 1,10-phenanthroline derivatives. [9] Amatore and Jutand showed that L_2PdX^- (X = Cl or Br) can be involved in the oxidative addition of aryl halides to palladium(0) complexes when reaction is carried out in the presence of halide anions.[10] *Cis*-$RPdXL_2$ isomerizes to most stable *trans*-$RPdXL_2$ can undergo syn-insertion into the C,C double bond of the in-plane coordinated alkene, to yield to generate η^2–organo-palladium complex. Then there is a carbopalladation or a migratory step which produces new σ- C-Pd and σ- C-C bond. The elimination of HPdX occur only after an internal rotation around the former double bond as it requires a β-hydrogen atom to be oriented *synplanar* with respect to the halopalladium residue so Heck reaction results stereoselective. After that alkene product and $L_2Pd(H)X$ are produced, and the presence of a base is necessary in order to transform the $L_2Pd(H)X$ into the starting $L_2Pd(0)$ complex and close the catalytic cycle. Typical bases used in the Heck reaction are tertiary amines (Et_3N, iPr_2NEt, etc.) or acetate or carbonate bases (AcONa, K_2C0_3, etc.). Heck reaction is reported to be a high regioselective reaction[11] using procedures that favour the coordination-insertion process via dissociation of the ligand. In the original work, the reaction was performed at high temperature in an aprotic polar solvent. More recently Jeffery[12] has developed new reaction condition using quaternary ammonium salts ($^nBu_4NCl$ o $^nBu_4NBr$) and K_2CO_3 or $NaHCO_3$ at room temperature.



Scheme 2

Amatore, Jutand and coll. studied the mechanistic details of Heck reaction using electrochemical methodologies and NMR, IR and UV[13] techniques. Thanks to this work they developed a more convincing mechanism for the reaction using the $Pd(OAc)_2/P(Ph)_3$ catalytic system (Scheme 3).

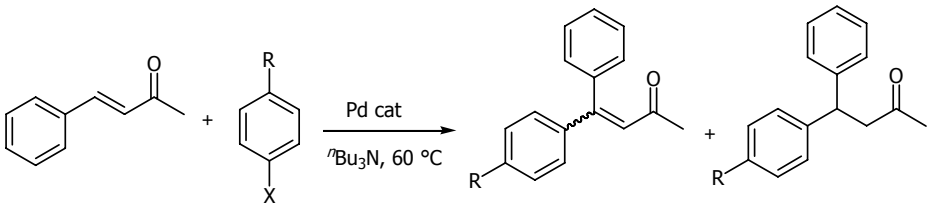


Scheme 3

2.1.1 Our recent acquisitions on Heck reaction

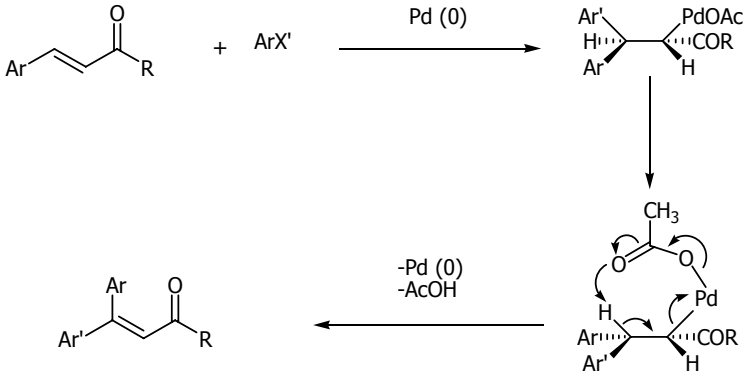
Because of the obvious huge amount of papers regarding the vinylic substitution produced since its discovery in the seventies', in this section only the results recently obtained in our laboratory will be underlined. In the late 1980s the reaction between benzalacetone and several *para*-substituted aryl iodides was chosen as model system to study the vinylic substitution of α,β-unsaturated β-substituted carbonyl compounds.[14] Using n-Bu_3N as base and Pd(II) salts

(Scheme 4), the main problem was the competition between vinylic substitution and conjugate addition. Hence efforts were made to minimise the formation of the latter.



Scheme 4

Good results were obtained using $^{n}Bu_4NCl$ in the presence of acetate salts, which were tentatively explained on the basis of an intramolecular attack on β-hydrogen by a palladium-bound acetate in the σ-alkylpalladium acetate intermediate (Scheme 5).[15]

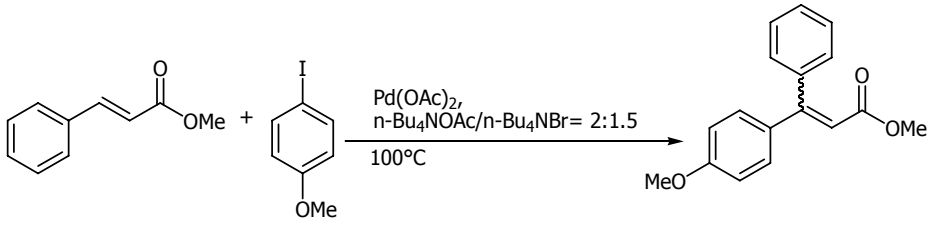


Scheme 5

Then, using vinyl triflate under these conditions vinylic substitution products were obtained in good yields with excellent regio and stereoselectivity. [16]

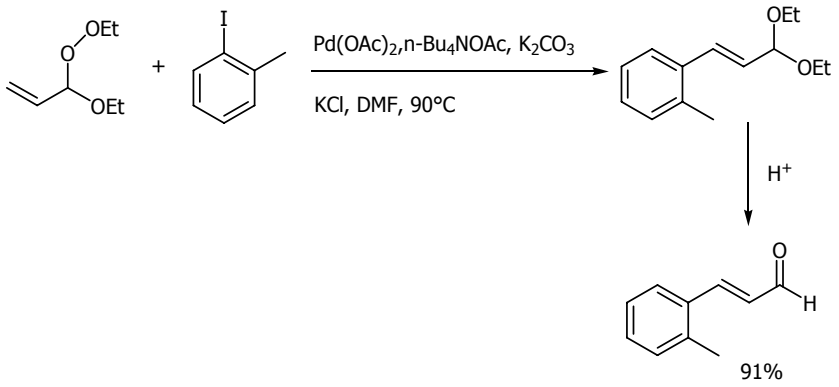
Thus, our studies conducted on the Heck reaction of disubstituted olefins,[17] α-substituted[18] and β-substituted α,β-unsaturated carbonyl compounds made us even more aware that many variables may influence the reaction outcome and that the presence of acetate anions[18d – 19g,h] may have a beneficial effect on the rate, yield and stereoselectivity of the vinylic substitution reaction.

As to the latter, evidence was attained that the presence of acetate anions in the Heck reaction of β-substituted α,β-unsaturated carbonyl compounds may favour the formation of vinylic substitution products with the original β-substituent on the same side of the carbonyl group. This was the basis of our domino Heck arylation/cyclization processes leading to the synthesis of quinolines, cardenolides, cumarines and quinolones using phosphine-free $Pd(OAc)_2$. [20c-d] We will describe the latter reaction in the following section. Taking advantage of this acetate effect, a simple and stereoselective synthesis of 3,3-diarilacrylates [20] from cinnammate esters was developed (Scheme 6).

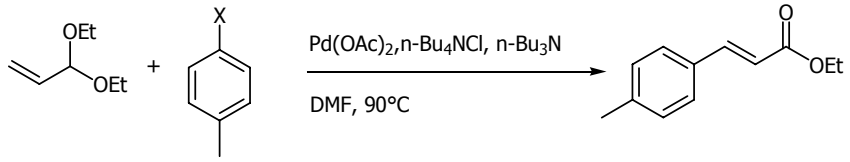


Scheme 6

Starting from acrolein diethyl acetal and varying the reaction conditions, a selective synthesis of cinnammaldehydes [20a] (Scheme 7) and propionic esters[20b] (Scheme 8) was attained.



Scheme7



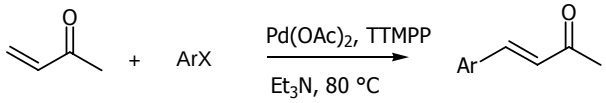
x =I,Br

x =I 81%

x =Br 74%

Scheme 8

More recently a highly selective synthesis of benzalacetones from butanone with aryl iodide has been developed (Scheme 9). In this case phosphine ligands have been found to affect the vinylic substitution to hydroarylation (conjugate addition type) ratio. The nature of the nitrogen base also plays a role in controlling the product selectivity. In the presence of $Pd(OAc)_2$ tris-(2,4,6-trimethoxyphenyl)phosphine and proton sponge the reaction affords exclusively vinylic substitution products usually in high to excellent yield. [21]



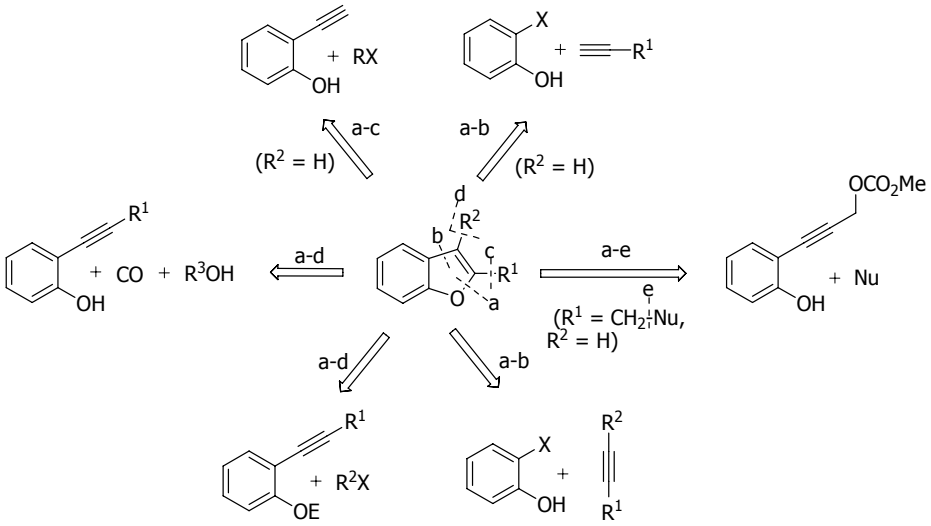
Scheme 9

2.2 Benzofurans core construction by Sonogashira reaction[22a]

Since Perkin synthesized benzo[*b*]furan in 1870 and Kraemer and Spilker discovered its presence in coal tar in 1890, the synthesis and functionalization of benzo[*b*]furans has been the subject of much research and a variety of general classical methods are now available which can be conveniently classified[22b-d] under the following headings: assembly of the heterocyclic ring from aromatic precursors, assembly of the heterocyclic ring from nonaromatic precursors, assembly of the heterocyclic ring from other heteroaromatic compounds, and fusion of the benzene ring to a furan precursor. Palladium-catalyzed syntheses of benzo[b]furans have been categorized into two main types: the de novo construction of the benzo[b]furan system from benzenoid precursors and the functionalization of preformed benzo[b]furan rings. The de novo

construction of the benzo[b]furan system usually involves the assembly of the furan nucleus on a benzenoid scaffold, via cyclization reactions. There are also examples of construction of the furan nucleus on heteroaromatic scaffolds.

A great deal of these studies is based on the utilization, as precursors, of compounds containing oxygen nucleophiles and carbon-carbon triple bonds both as parts of the same molecule or as separate components. In Scheme 10 is reported retro-synthetic representation of the alkyne-based palladium-catalyzed assembly of the benzo[b]furan ring. The furan nucleus was assembled even by using precursors containing oxygen nucleophiles and carbon-carbon double bonds via intramolecular and intermolecular cyclization. In addition to alkyne- and alkene-based procedures leading to the assembly of the furan nucleus on a benzenoid scaffold, other less frequently applied strategies for the de novo synthesis of the benzo[b]furan system involve the intramolecular Buchwald/Hartwig C-O bond forming process[23] and the construction of the benzenoid ring on a furan scaffold.



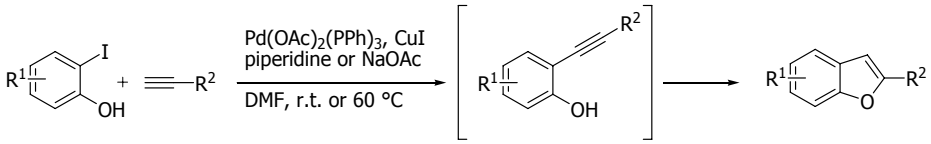
Scheme 10

As to the functionalization of the preformed benzo[b]furan system, two main trends can be recognized: (a) functionalization via benzofuryl halides or triflates and (b) functionalization via organometallic derivatives such as benzofurylstannanes, benzofurylboronic acids and benzofurylzinc compounds. Examples of functionalization via direct activation of C-H bonds have

also been reported. We focused principally on alkyne-based palladium-catalyzed assembly of the benzo[b]furan ring and in particular the synthetic way corresponding to disconnection a-b, a-c and a-d.

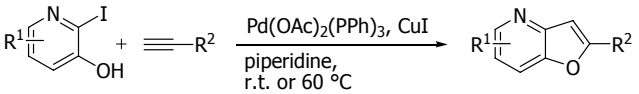
Disconnection a-b

The first example of a palladium based synthesis of 2-substituted benzo[*b*]furans from *o*-halophenols and terminal alkynes was described by Cacchi et al. in the mid eighties. [24] The reaction is considered to involve the palladium-catalyzed coupling of 1-alkynes with *o*-iodophenols, followed by the cyclization of the resultant coupling intermediates (scheme 11). This process allowed to channel the copper-mediated approach described by Castro et al.[25] usually requiring strong conditions (typically 120 °C in DMF or pyridine), into a mild procedure that can accommodate a variety of functional groups. The coupling reaction was best carried out under Sonogashira conditions[26] and piperidine was usually employed as the base. However, with ethyl propynoate as the terminal alkyne, the corresponding benzo[b]furans was obtained (in low yield) only by using NaOAc, reported by us to be the optimal base in the coupling of ethyl propynoate with vinyl triflates. [27]



Schema 11

Extending the substrate scope of the reaction, we showed in the same work that the palladium catalyzed coupling/cyclization approach could be applied to the synthesis of furo[3,2-*b*]pyridines (Scheme 12).

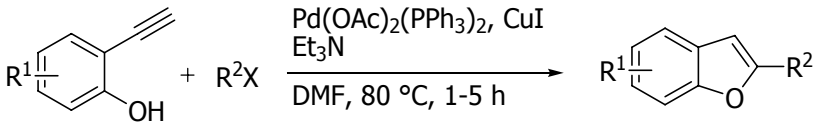


Schema 12

The potential of this palladium-based approach to benzo[*b*]furans has not gone unnoticed and attracted the attention of several groups of investigators who expanded the scope of the reaction by incorporating different substrates, bases, solvents, ligands and palladium precatalysts. The methodology has also been applied to the synthesis of a variety of natural products. The benzo[*b*]furan ring was suggested to arise from the intramolecular cyclization of an organopalladate intermediate. In addition to solution phase synthesis, the palladium-catalyzed coupling-cyclization protocol was utilized both in solid-phase synthesis and with supported palladium catalysts. A solventless, microwave-enhanced coupling-cyclization of *o*-iodophenols with terminal alkynes on potassium fluoride doped alumina in the presence of palladium powder, cuprous iodide , and triphenylphosphine led to the formation of 2-substituted benzo[*b*]furans in moderate yield. [28]

Disconnection a-c

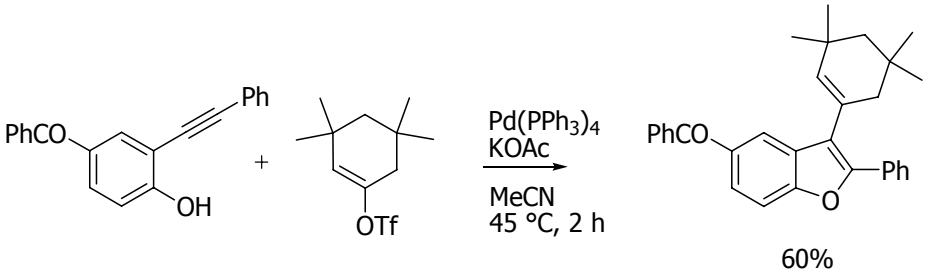
It was developed an alternative methodology in which 2-vinyl and 2-arylbenzo[*b*]furans can be prepared from the same acetylenic building block: *o*-ethynylphenols. [29] *o*-Ethynylphenols were prepared via palladium-catalyzed coupling of *o*-iodophenols (or *o*-halophenylacetates) with trimethylsilylacetylene, followed by a desilylation step. This benzo[*b*]furan synthesis features a palladium-catalyzed reaction of *o*-ethynylphenols with vinyl and aryl triflates or halides followed by the cyclization of the resultant coupling intermediate (Scheme 13).



Scheme 13

Disconnection a-d

As an extension of our palladium-catalyzed indole synthesis from *o*-alkynyltrifluoroacetanilides,[30] in 1996 we developed a new approach to the construction of the functionalized furan ring of the benzo[*b*]furan system from *o*-alkynylphenols[9]. Though the desired 2,3-disubstituted benzo[*b*]furans were usually isolated in low to moderate yields under the conditions used (the propensity of *o*-alkynylphenols to cyclize to simple 2-substituted benzo[*b*]furans was in some cases a significant side reaction), this synthesis provided a straightforward new route to this class of compounds (Scheme14).

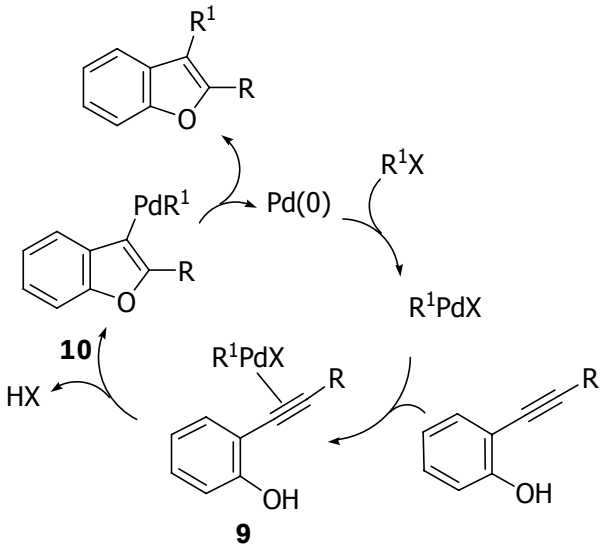


Scheme 14

The reaction is considered to proceed through the following basic steps (Scheme 15): (a) coordination of *o*-alkynylphenols to organopalladium(II) complexes (generated *in situ* via oxidative addition of organic halides or triflates to palladium(0) species and exemplified as "R^1PdX" in Scheme 21) to give the π-alkyne-organopalladium complexes **9**, (b) intramolecular nucleophilic attack of the oxygen across the activated carbon-carbon triple bond to afford the oxypalladation adduct **10**, (c) reductive elimination reaction which forms a new carbon-carbon bond and regenerates the active palladium(0) catalyst.

Flynn et al.[31] tried to improve this protocol developing a one-pot multi-component coupling procedure and researchers at VivoQuest. [32] focused on the optimization of the original conditions [29] in the attempt to prevent the formation of 2-substituted benzo[*b*]furan. In particular, they explored the role of a variety of catalyst systems on the reaction outcome. Using the reaction of *o*-(phenylethynyl)phenol with *p*-iodoanisole as the model system, they obtained unsatisfactory results with $Pd(PPh_3)_4$, $Pd_2(dba)_3$, $Pd_2(dba)_3/P(t\text{-}Bu)_3$ and $Pd_2(dba)_3$/dppf

in the presence of K_2CO_3. However, switching to the $Pd_2(dba)_3$/bipyridine (bpy) catalyst system afforded the desired 2,3-disubstituted benzo[*b*]furan in 70% yield and a variety of 2,3-disubstituted benzofurans were prepared under these conditions in good to high yield (Scheme 23).



Scheme 15

Electron-poor aryl iodides gave the best results, presumably due to the favorable effect of electron-withdrawing substituents on the oxidative addition step. Using modified reaction conditions for the cyclization of *o*-alkynylphenols with aryl iodides (2.2 equiv of $Pd_2(dba)_3$, 4.4 equiv of bpy, ArI, CsOAc, DMF, 25 °C, 48 h), this research group prepared a 210-membered 2-substituted 3-arylbenzo[*b*]furan library via a solid-phase synthesis.

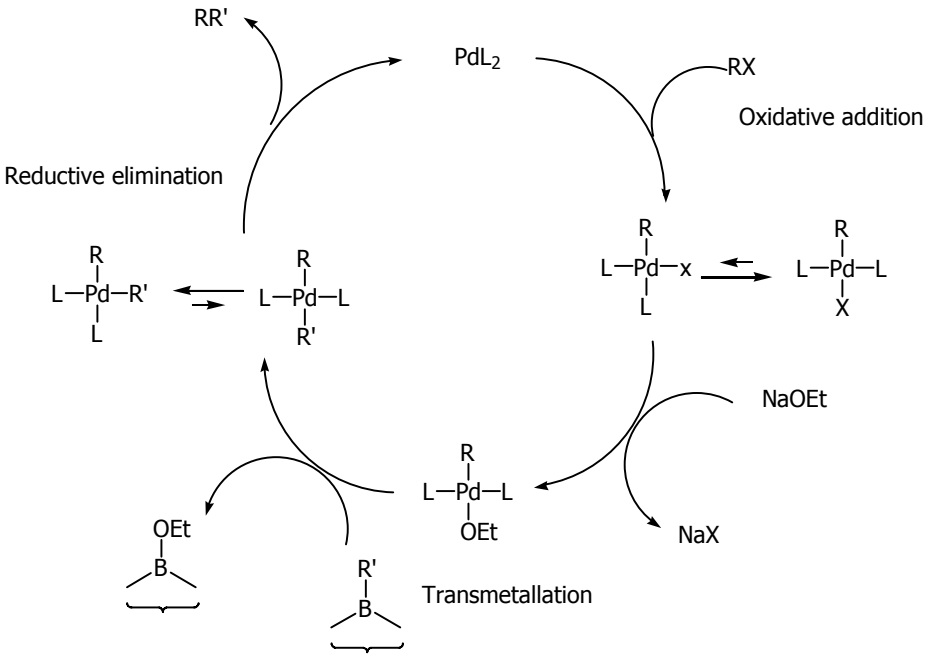
2.3 Suzuki reaction

The palladium-catalyzed coupling of organic halides or triflates with organoboranes under basic conditions (Suzuki-Miyaura coupling) provides a highly versatile method for the construction of new carbon-carbon bonds that tolerates many functional groups. [33] By analogy to related processes [34] the coupling of organoboranes is believed to proceed through a catalytic cycle involving three basic steps:[35] (1) the oxidative addition of the carbon electrophile to the zerovalent and coordinationally unsaturated PdL_2, where L is normally a phosphine ligand such as PPh_3, (2) the transmetalation of a nucleophilic carbon from boron to the R'PdXL2, and (3) the rapid reductive elimination of the cross-coupling product with the regeneration of the PdL_2 catalyst (Scheme 16). It is the transmetalation step that differentiates one organometallic process from another. Oxidative addition is known to proceed with retention of stereochemistry with vinyl halides and with inversion with allylic and benzylic halides[36] and intially gives a cis complex that rapidly isomerizes to its trans isomer.[37]

Organoboron compounds are highly covalent in character, and do not undergo transmetallation readily in the absence of base. The role of the base during this step is unresolved, Boron "ate" complexes, formed via quaternization of the boron with a negatively charged base, are frequently invoked. As in others palladium catalysed reaction relative reactivity of leaving groups is I->OTf->Br-»CI-.Then, isomerization to the cis complex is required before reductive elimination can occur. Relative rates of tis step from palladium(II) complexes: aryl-aryl > alkyl-aryl > n-propyl-n-propyl > ethyl-ethyl > methyl-methyl.[38]

The most commonly used system is $Pd(PPh_3)_4$, but other palladium sources have been used including Pd^{II} pre-catalysts that are reduced to the active Pd^0 in situ (e.g. $Pd_2(dba)_3$ + PPh_3, $Pd(OAc)_2$ + PPh_3 and $PdCl_2$(dppf)).

Besides "Ligand-free" conditions, using $Pd(OAc)_2$, have been developed. Side reactions often associated with the use of phosphine ligands (phosphonium salt formation and aryl-aryl exchange between substrate and phosphine) are thus avoided. [39]


RR'
PdL2
RX
Oxidative addition
Reductive elimination
R
L—Pd—x
L
R
L—Pd—L
X
NaOEt
NaX
R
L—Pd—L
OEt
OEt
B
R'
B
Transmetallation
R
L—Pd—R'
L
R
L—Pd—L
R'

Scheme 16

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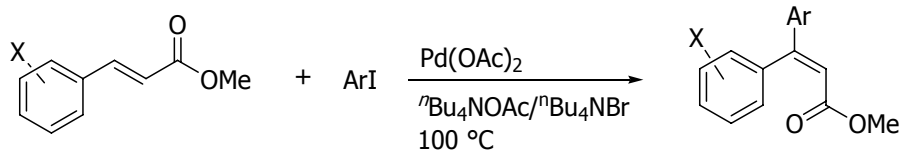
SYNTHESIS OF COUMARINS IN A MOLTEN TETRABUTYLAMMONIUM ACETATE/TETRABUTYLAMMONIUM BROMIDE MIXTURE THROUGH A DOMINO HECK REACTION/CYCLIZATION PROCESS

Introduction

During our continuing studies on the Heck reaction of disubstituted alkenes we have found that the presence of acetate anions in the Heck reaction of β-substituted α,β-unsaturated carbonyl compounds may favor the formation of vinylic substitution products with the original β-substituent on the same side of the carbonyl group.[1] Acetate anions might be involved in the irreversible displacement of palladium from σ-alkylpalladium adducts suppressing isomerizations based on the well-known elimination-readdition of hydridopalladium species. [1a]

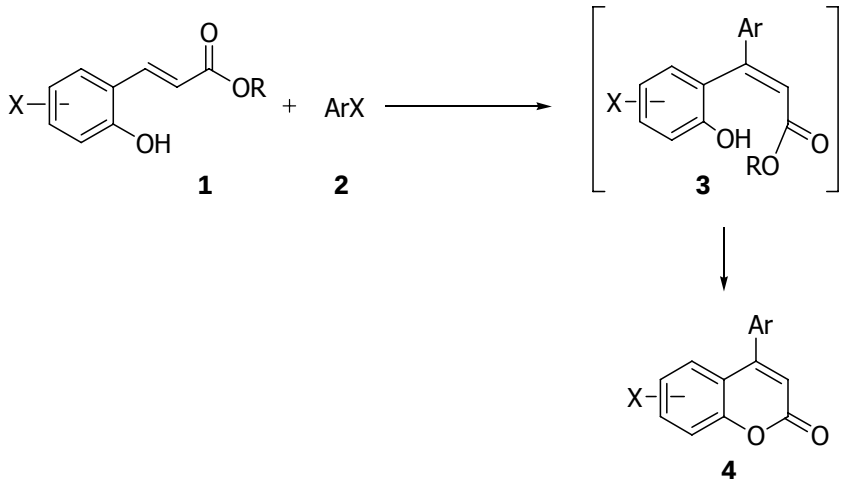
Recently, we have taken advantage of this acetate effect to develop a simple and stereoselective synthesis of β,β-diarylacrylates from cinnamate esters. [2] In particular, aryl iodides were treated with methyl 3-arylacrylates in a molten $^{n}Bu_4NOAc/^{n}Bu_4NBr$ mixture in the presence of $Pd(OAc)_2$ to afford a variety of β,β-diarylacrylates, usually in good to high yield (Scheme 1). Subsequently, the reaction has been extended to aryl bromides. [3]



Scheme1

The reaction (which most probably involves palladium nanoparticles stabilized by quaternary ammonium ions) [4] appeared to us particularly promising for the development of domino vinylic substitution/cyclization processes. In fact, because of the *cis* configuration - in the Heck product - of the carbonyl group and the preexisting β-substituent, a cyclization reaction would be expected to follow the initial vinylic substitution in the presence of *ortho* nucleophiles in the

original β-aryl unit. In particular, we envisioned that this domino process could constitute a new approach to coumarins (Scheme 2).



Scheme 2

The coumarin motif is abundant in a number of complex natural products exhibiting a broad range of pharmacological activities, [5] including anticancer[6] and anti-HIV[7] activities. Coumarin derivatives have also been used as luminescent probes,[8] photostable laser dyes,[9] and triplet sensitizers.[10] However, the synthesis of this class of compounds currently relies on classical Perkin, [11] Pechmann, [12] Knoevenagel[13] reactions, which suffer from major drawbacks (drastic conditions, stoichiometric amounts of Lewis or mineral acids, multistep protocols, troublesome work-up procedures). Attempts to expand the synthetic approach to functionalized coumarins by using transition metal-catalyzed procedures have been reported. [14] However, some of them are of limited scope, and most of the palladium-catalyzed procedures rely on the functionalization of a preformed coumarin nucleus[14d-m] or are limited to alkyne-based cyclization reactions. [14n-r]

Herein we report that the reaction of readily available methyl and butyl 3-(*o*-hydroxyaryl)acrylates with aryl iodides and bromides in the presence of $Pd(OAc)_2$ (no phosphine

ligands are required) in a $^{n}Bu_4NOAc/^{n}Bu_4NBr$ mixture, constitutes an efficient new route to 4-aryl coumarins bearing a variety of functional groups.

Results and discussion

Cinnamic acid esters **1** were readily prepared in 70-90% yields through the palladium-catalyzed reaction of *o*-iodophenols with methyl or butyl acrylate[15] [1 equiv of *o*-iodophenol, 1.3 equiv of acrylate ester, 0.01 equiv of $Pd(OAc)_2$, 1.3 equiv of Et_3N, MeCN, 80-100 °C under argon].

Reaction conditions successfully employed by us in the synthesis of β,β-diarylacrylates [1 equiv of cinnamate, 1.5 equiv of aryl iodide and 0.05 equiv of $Pd(OAc)_2$ in a $^{n}Bu_4NOAc/^{n}Bu_4NBr$ mixture at 100 °C] were used when the domino process was attempted using *p*-iodoanisole and methyl 3-(*o*-hydroxyphenyl)acrylate as the model system. Pleasingly, the desired coumarin product **4a** was isolated in 82% yield after 8 h.

Control experiments were performed to evaluate the efficiency of this protocol. Some results from this study are summarized in Table 1 and show that the process could be successfully extended to *p*-bromoanisole (Table 1, entry 2). Notably, it could not be driven to completion under conditions using a molecular solvent such as DMF as the reaction medium (Table 2, entries 3 and 4). The use of butyl 3-(*o*-hydroxyphenyl)acrylate gave **4a** in higher yield (Table 1, entry 5). No significant amounts, if any, of the vinylic substitution intermediate were detected when the reaction was monitored by TLC and HPLC analysis (the same trend has been observed with other aryl halides and acrylate esters), both with the methyl and the butyl ester. This suggests that the cyclization of vinylic substitution intermediates to coumarin is the fast step and that displacement of the more basic butoxide anion does not affect the reaction course to a large extent.

Table 1. Aryl Halides, Solvents and 3-(*o*-Hydroxyphenyl)acrylates in the Synthesis of **4a**.[a]

entry	R acrylate **1**	aryl halide **2**	conditions	yield of **4a** (%)[b]
1	Me	*p*-MeO-C_6H_4-I	$^nBu_4NOAc$ (2.1 equiv), $^nBu_4NBr$ (1.5 equiv)	82
2	Me	*p*-MeO-C_6H_4-Br	$^nBu_4NOAc$ (2.1 equiv), $^nBu_4NBr$ (1.5 equiv)	78
3	Me	*p*-MeO-C_6H_4-Br	AcOK (2.5 equiv), DMF (1.5 mL)	traces[c]
4	Me	*p*-MeO-C_6H_4-Br	$NaHCO_3$ (2.5 equiv), $^nBu_4NCl$ (1 equiv), DMF (1.5 equiv)	22[d]
5	^{n}Bu	*p*-MeO-C_6H_4-Br	$^nBu_4NOAc$ (2.1 equiv), $^nBu_4NBr$ (1.5 equiv)	88[e]

[a] Unless otherwise stated, reactions were run in the presence of 5 mol % of $Pd(OAc)_2$ at 100 °C for 8 h by using 1.5 equiv of **2** and 1 equiv of **1**.
[b] Yields are given for isolated products.
[c] The starting acrylate ester was recovered in 78% yield.
[d] The starting acrylate ester was recovered in 56% yield.
[e] 6 h.

Therefore, we focused primarily on the use of the more convenient aryl bromides when the substrate scope of this synthesis was explored. Both butyl and methyl esters were employed. Our preparative results are shown in Table 2.

Butyl esters were usually found to provide better results than methyl esters with electron-rich and slightly electron-poor aryl halides. Similar yields were instead obtained with strongly electron-poor aryl halides. For example, the coumarin derivative was isolated in 35-37% yield with p-bromobenzaldehyde both with the methyl acrylate and the butyl acrylate (Table 2, entries 13 and 14).

As to the aryl halide partner, a variety of electron-rich and slightly electron-poor aryl bromides react well in the ionic liquid medium to provide the desired coumarin derivatives usually in good to high yields. Moderate yields were instead obtained with aryl bromides containing strongly electron-withdrawing substituents.

Table 2. Synthesis of 4-Aryl Coumarins **4** from 3-(*o*-Hydroxyphenyl)acrylates **1** and Aryl Iodides and Bromides **2**.[a]

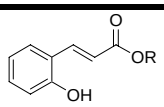
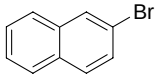
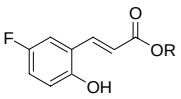
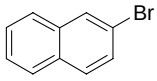
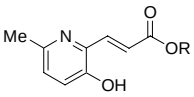
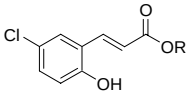
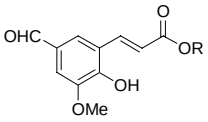
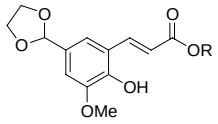
entry	3-(*o*-hydroxyphenyl) acrylate ester 1			aryl halide 2	t (h)[b]	yield of 4 (%)[c]
1		R = Me	**1a**	*p*-MeO-C_6H_4-Br	8	**4a** 78
2		R = Bu^n	**1b**	*p*-MeO-C_6H_4-Br	8	**4a** 88
3		R = Me	**1a**	*m*-MeO-C_6H_4-Br	8	**4b** 75
4		R = Bu^n	**1b**	*p*-MeCOO-C_6H_4-Br	2	**4c** 70[d]
5		R = Me	**1a**	*p*-Me_2N-C_6H_4-Br	7	**4d** 74
		R = Bu^n	**1b**	*p*-Me_2N-C_6H_4-Br	7	**4d** 98
6		R = Me	**1a**	*p*-Me-C_6H_4-Br	10	**4e** 75
7		R = Me	**1a**	*p*-F-C_6H_4-Br	24	**4f** 75
8		R = Me	**1a**	*m*-F-C_6H_4-Br	31	**4g** 70
9		R = Me	**1a**	*p*-^{t}Bu-C_6H_4-Br	30	**4h** 61
10		R = Bu^n	**1b**	*p*-^{t}Bu-C_6H_4-Br	10	**4h** 82
11		R = Bu^n	**1b**	*p*-MeCONH-C_6H_4-Br	24	**4i** 77
12		R = Bu^n	**1b**	*o*-MeCONH-C_6H_4-Br	24	-[e]
13		R = Me	**1a**	*p*-CHO-C_6H_4-Br	24	**4j** 35
14		R = Bu^n	**1b**	*p*-CHO-C_6H_4-Br	24	**4j** 37
15		R = Me	**1a**	*p*-Ph-C_6H_4-Br	8	**4k** 68
16		R = Bu^n	**1b**	*p*-Ph-C_6H_4-Br	10	**4k** 83
17		R = Me	**1a**	*m*-CF_3-C_6H_4-Br	31	**4l** 67[f]
18		R = Bu^n	**1b**	*p*-Br-C_6H_4-Br	24	**4m** 30[g]
19		R = Bu^n	**1b**	*p*-Br-C_6H_4-I	33	**4m** 50[g]
20		R = Bu^n	**1b**			**4n** 65[h]
21		R = Me	**1c**	*p*-Ph-C_6H_4-Br	48	**4o** 68
22		R = Me	**1c**		24	**4p** 70

Table 2. Synthesis of 4-Aryl Coumarins **4** from 3-(*o*-Hydroxyphenyl)acrylates **1** and Aryl Iodides and Bromides **2**.[a] (Continue)

entry	3-(*o*-hydroxyphenyl) acrylate ester 1			aryl halide 2	t (h)[b]	yield of 4 (%)[c]
23		R = Me	**1c**	*p*-MeO-C_6H_4-I	4.5	**4q** 86
24		R = Me	**1d**	*p*-MeO-C_6H_4-I	26	**4r** 37
25		R = Bu^n	**1e**	*p*-MeO-C_6H_4-I	30	**4r** 36
26		R = Me	**1f**	*p*-MeO-C_6H_4-I	5	**4s** 82
27		R = Me	**1g**	*p*-MeO-C_6H_4-Br	5.5	-
28		R = Me	**1h**	*p*-MeO-C_6H_4-Br	5.5	**4t** 70[i]

[a] Unless otherwise stated, reactions were run in the presence of 5 mol % of $Pd(OAc)_2$ at 100 °C by using 1.5 equiv of **2** and 1 equiv of **1**. [b] Reaction times were not optimized. [c] Yields are given for isolated products. [d] Isolated as 4-(*p*-hydroxyphenyl) derivative. [e] The starting aryl bromide was recovered in 63% yield. [f] In the presence of 2.5 equiv of aryl halide. With 1.5 equiv of aryl halide, **4l** was isolated in 53% yield. [g] With 3 equiv of aryl halide. [h] **1b** was recovered in 15% yield. [I] Isolated as the formyl derivative, after acid work-up

As far as the ß-aryl group is concerned, good to excellent results can be obtained when it contains electron-donating and weak electron-withdrawing substituents. Strongly electron-withdrawing substituents para to the o-hydroxy group appear to hamper the reaction. For example, when 1g was subjected to our standard conditions, a complex reaction mixture was formed which we have not further investigated (Table 2, entry 27). However, an appropriately protected aldehydic acrylate (Table 2, entry 28) gave the desired product in 70% yield. Moderate yields were obtained with heterocyclic analogues of 3-(o-hydroxyphenyl)acrylates (Table 2, entries 24 and 25).

Interestingly, reactions did not have to be carried out under an argon atmosphere. It appears that the catalytic activity is maintained for a relatively long time even in the presence of oxygen.

Conclusion

In conclusion, we have developed a convenient straightforward route for the construction of the functionalized lactone ring incorporated into the coumarin system from readily available starting materials that may represent a useful alternative to classical methods and compares well with known palladium-based procedures.

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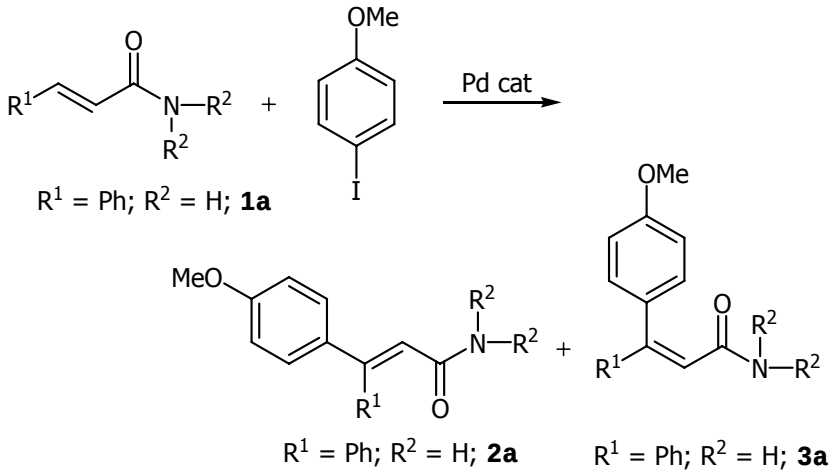
THE HECK REACTION OF β-ARYLACRYLAMIDES. AN APPROACH TO 4-ARYL-2-QUINOLONES

Introduction

The Heck reaction of β-substituted α,β-unsaturated carbonyl compounds with aryl halides may serve as a valuable method for the preparation of highly functionalized olefin systems. Because of this, the preparation of β,β-disubstituted derivatives from β-substituted α,β-enals and -enones,[1] and α,β-unsaturated esters[2] have been the subject of several investigations, with the achievement of a stereoselective synthesis being a major target. Indeed, whereas excellent regioselectivity was always observed (with vinylic substitution products at the β-position being usually the sole products), the stereochemistry of the reaction was found to depend strongly on reaction conditions. Surprisingly, very few has been done with β-substituted acrylamides.

Results and discussion

We described the tendency of cinnamamide to afford preferentially the corresponding vinylic substitution product in the palladium catalyzed reaction with iodobenzene in the presence of triethylamine and formic acid as compared to cinnamaldehyde and benzalacetone (and a variety of α,β-enones) which gave conjugate addition type derivatives as the main products under the same conditions.[3] A β,β-diarylacrylamide was prepared adapting the Heck reaction to solid phase conditions, but the stereochemistry of the Heck product was not established.[4] More recently, Nájera et al. described the preparation of two β,β-diarylacrylamides via vinylic substitution of β-substituted acrylamides in a study devoted to explore Heck reactions of α,β-unsaturated carbonyl compounds in aqueous media.[5] On the other hand, theβ,β-diarylacrylamide motif is present in a variety of biologically active molecules.[6] Therefore, it appeared to us of interest to explore in more detail the Heck reaction of this class of compounds. The reaction of *p*-iodoanisole with cinnamamide[7] **1a** in the presence of 0.05 equiv of $Pd(OAc)_2$ was initially examined as the model system (Scheme 1).



Scheme 1

Part of our optimization work using different bases, solvents and additives is displayed in Table 1. Under a variety of reaction conditions, good chemical yields were observed but the stereochemical outcome was only moderate (Table 1, entries 1-3). Under Jeffery conditions[8] no vinylic substitution product was isolated (Table 1, entry 4). Using KOAc as base and omitting Bu_4NCl produced the vinylic substitution product in good yield and satisfactory stereoselectivity (Table 1, entry 5). Switching to a Bu_4NOAc/Bu_4NBr molten salt mixture (these conditions gave excellent conversions and stereochemical control with cinnamate esters) [2g] led to a moderate conversion and low **2a** to **3a** molar ratio (Table 1, entry 8). The best result in terms of yield and **2a** to **3a** molar ratiowas obtained when the reaction was carried out in triethylamine (Table 1, entry 7). The stereochemistry of **2a** and **3a** [obtained as an approximately 20:80 mixture when prepared from iodo-benzene and β-(p-methoxyphenyl)acrylamide] was as assigned by NOE experiments. That of the other vinylic substitution products (vide infra) has been assigned based on these data.

Table 1. Bases, Additives, and Solvents in the Palladium-Catalyzed Reaction of Cinnamamide **1a** with *p*-Iodoanisole.[a]

entry	base	additive	solvent	time (h)	overall yield %	2a:3a	yield % 1a
1	Et_3N (3 equiv)	-	DMF	48	82	76:24	15
2	Et_3N (3 equiv)	-	THF	24	70	74:26	25
3	Et_3N (3 equiv)	-	AcOEt	24	67	74:26	27
4	K_2CO_3 (2 equiv)	Bu_4NCl (1 equiv)	DMF	96	-		68
5	KOAc (2 equiv)	-	DMF	96	71	84:16	20
6	Bu_4NOAc (2 equiv}	-	DMF	48	54	68:32	18
7	Et_3N (5 equiv)	-	-	12	92	83:17	-
8	Bu_4NOAc (3 equiv)	Bu_4NBr (3 equiv)	-	24	60	70:30	20

[a] All reactions were carried out on a 0.5 mmol scale at 100 °C under an argon atmosphere using 1 equiv of **1a**, 1.5 equiv of *p*-iodoanisole and 0.05 equiv of $Pd(OAc)_2$ in 1.5 mL of solvent.

Thus, these conditions were used when the procedure was extended to the reaction of other β-arylacrylamides with *p*-iodoanisole (Table 2) and ethyl *p*-iodobenzoate (Table 3), models of electron-rich and electron-poor aryl iodides, respectively. Using *p*-iodoanisole as the aryl partner, β,β-diarylacrylamides were produced in high yields and with satisfactory stereoselectivity, the highest stereoselectivity being observed with the *N,N*-dimethyl-β-arylacrylamides (Table 2, entries 2, 3, 6, 9, 11, 13, 14) and β-(*o*-substituted aryl)acrylamides (Table 2, entries 4, 7-9).

strong tendency to give *p,p'*-diethoxycarbonyl biphenyl, the biaryl-product formed via a homocoupling process. With the *N*-unsubstituted β-arylacrylamides that we have tested, *p,p'*-diethoxycarbonyl biphenyl was isolated in 20-37% yields and the desired vinylic substitution products were obtained in moderate yields (Table 3, entries 2, 5 and 10). Since it has been reported that formation of homocoupling biaryl products - a competitive side reaction assumed to require a bimolecular transmetalation of σ-arylpalladium intermediates - can be limited by decreasing the catalyst loading, [9] we decided to conduct the reaction using lower amounts of

catalyst. Indeed, decreasing the catalyst loading to 0.01 equiv led to a remarkable increase of yields at the expense of biaryl formation (Table 3, compare entries 3, 6, 11 with entries 2, 5, 10 respectively).

Table 2. The Palladium-Catalyzed Heck Reaction of β-Arylacrylamides **1** with p-Iodoanisole.[a]

entry	β-arylacrylamide **1**			time (h)	**2**	**3**
	R^1	R^2			yield %[b]	yield %[b]
1	Ph	H	**1a**	24	**2a** 66	**3a** 16
2	Ph	Me	**1b**	12	**2b** 74)	**3b** 8
3	*p*-Me-C_6H_4	Me	**1c**	48	**2c** 79	**3c** 17
4	*o*-MeO-C_6H_4	H	**1d**	12	**2d** 91	**-**
5	*m*-MeO-C_6H_4	H	**1e**	24	**2e** 56	**3e** 14
6	*m*-MeO-C_6H_4	Me	**1f**	48	**2f** 64	**3f** 24
7	*o*-Me-C_6H_4	H	**1g**	24	**2g** 74	**-**
8	*o*-Br-C_6H_4	H	**1h**	12	**2h** 87	-
9	*o*-Br-C_6H_4	Me	**1i**	24	**2i** 70	-
10	*m*-F-C_6H_4	H	**1j**	24	**2j** 57	**3j** 18
11	*m*-F-C_6H_4	Me	**1k**	48	**2k** 80	**3k** 8
12	*m*-CF_3-C_6H_4	H	**1l**	24	**2l** 68	**3l** 12
13	*m*-CF_3-C_6H_4	Me	**1m**	48	**2m** 83	**3m** 9
14	*p*-MeCO-C_6H_4	Me	**1n**	36	**2n** 84	**3n** 10

a All reactions were carried out on a 0.5 mmol scale at 100 °C under an argon atmosphere using 1 equiv of 1, 1.5 equiv of p-iodoanisole, 3 equiv of Et3N and 0.05 equiv of Pd(OAc)2.
b Yields are given for isolated products.

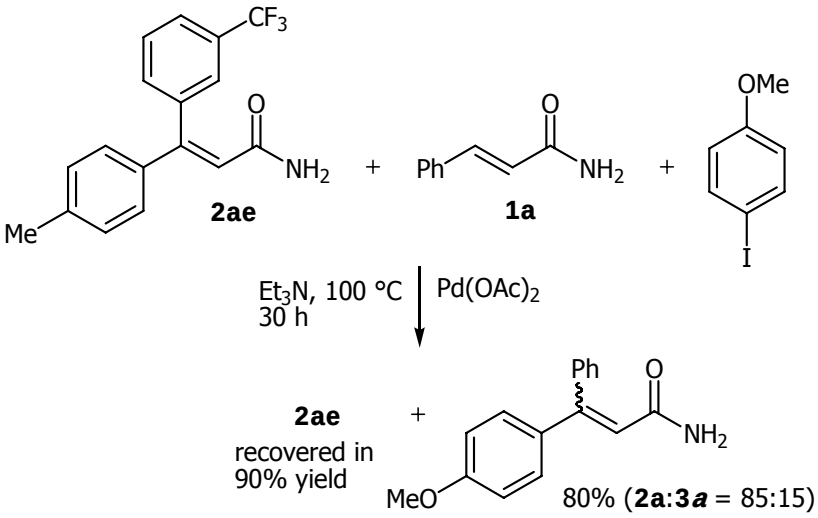
Reactions with ethyl *p*-iodobenzoate, under the conditions used with *p*-iodoanisole, showed a As to the stereochemical outcome, equilibration following the Heck arylation might account for the formation of mixtures of stereoisomers. In the present reaction, however, it appears that stereoisomers are generated during the vinylic substitution event through the well known elimination-reverse addition-elimination of HPd species and that no equilibration occurs after the vinylic substitution products are formed. This view is supported by the following experiment. A pure sample of 2ae, prepared via the reaction of **1a** with p-iodotoluene, was

subjected to the conditions producing vinylic substitution products in the presence of 1a and p-iodoanisole (Scheme 2). The 3,3-diarylacrylamide product, formed via the reaction of **1a** with p-iodoanisole, was isolated in 80% yield as an approximately 85:15 E:Z mixture (a result similar to that reported in Table 2, entry 1). Compound 2ae was recovered in almost quantitative isolated yield and its stereochemistry was maintained, even under prolonged heating.

Table 3. The Palladium-Catalyzed Heck Reaction of β–Arylacrylamides **1** with Ethyl p-Iodobenzoate.[a]

entry	β-arylacrylamide **1**			**2** yield %	**3** yield %[b,d]
	R^1	R^2			
1	*o*-MeO-C_6H_4	H	**1d**	**2o** 78	-
2[d]	*m*-MeO-C_6H_4	H	**1e**	**2p** 56	**3p** 14 (5)
3	*m*-MeO-C_6H_4	H	**1e**	**2p** 68	**3p** 13 (-)
4	*m*-MeO-C_6H_4	Me[e]	**1f**	**2q** 74	**3q** 6
5[d]	*p*-MeO-C_6H_4	H	**1j**	**2r** 37	**3r** 11 (20)
6	*p*-MeO-C_6H_4	H	**1j**	**2r** 62	**3r** 14 (-)
7	*p*-MeO-C_6H_4	Me[e]	**1o**	**2s** 88	**3s** 7
8[d]	*o*-Me-C_6H_4	H	**1g**	**2t** 90	-
9	*o*-Me-C_6H_4	H	**1g**	**2t** 91	-
10[d]	Ph	H	**1a**	**2u** 36	**3u** 16 (30)
11	Ph	H	**1a**	**2u** 74	**3u** 13 (-)
12	Ph	Me[e]	**1b**	**2v** 91	**2v** 6
13[d]	*m*-F-C_6H_4	H	**1j**	**2w** 60	**3w** 10 (32)
14	*m*-F-C_6H_4	Me	**1k**	**2y** 86	**3y** 10
15[d]	*m*-CF_3-C_6H_4	H	**1l**	**2z** 48	**3z** 9 (37)
16	*m*-CF_3-C_6H_4	Me[e]	**1m**	**2ab** 82	**3ab** 8
17	*o*-Br-C_6H_4	H	**1h**	**2ac** 82	**-**
18	*p*-MeCO-C_6H_4	Me[e]	**1n**	**2ad** 65	**-**

[a] Unless otherwise stated, reactions were carried out on a 0.5 mmol scale at 100 °C for 24 hunder an argon atmosphere using 1 equiv of **1**, 2.5 equiv of ethyl *p*-iodobenzoate, 5 equiv of Et_3N and 0.01 equiv of $Pd(OAc)_2$. [b] Yields are given for isolated products.[c] Figures in parentheses refer to isolated homocoupling products.[d] In the presence of 1.5 equiv of ethyl *p*-iodobenzoate, 3 equiv of Et_3N and 0.05 equiv of $Pd(OAc)_2$.[e] 36 h.



Scheme 2

Electronic effects due to the β-aryl groups in the carbopalladation adduct appear to play a role in controlling the stereochemical outcome. In particular, it seems that β-substituents containing electron-withdrawing groups tend to afford higher stereoselectivity. For example, a relatively low stereoselectivity was observed in the reaction of **1c** with *p*-iodoanisole - the carbopalladation adduct contains two electron-rich β-substituents (Table 2, entry 3) – whereas **2ad** was formed as the sole stereoisomer in the reaction of **1n** with ethyl *p*-iodobenzoate (Table 3, entry 18). In the latter case, the carbopalladation adduct contains two electron-poor β-substituents.

The general higher diastereoselectivity observed with *N,N*-dimethyl-β-arylacrylamides as compared to *N*-unsubstituted β-arylacrylamides may be due to the stronger tendency of the disubstituted amide group to coordinate to palladium[10] (Figure 1). This coordinating effect could disfavor the reverse addition of HPdX generating the carbopalladation adduct with the palladium atom close to the β-substituents.

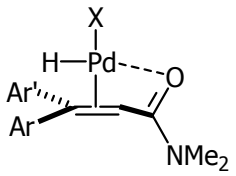


Figure 1

The exclusive formation of the trisubstituted olefin containing the original β-substituent on the same side of the carbon-carbon double bond as the amide group when β-(*o*-substituted aryl)acrylamides are used as substrates is also remarkable. Most probably it is due to the relative instability of the adduct B, which would form from A via elimination-reverse addition of HPdX, in the presence of an *ortho* substituent.

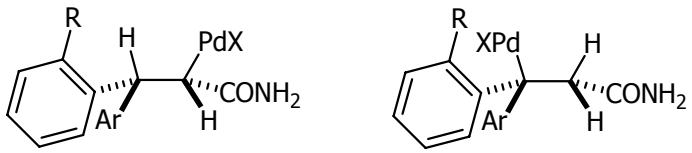
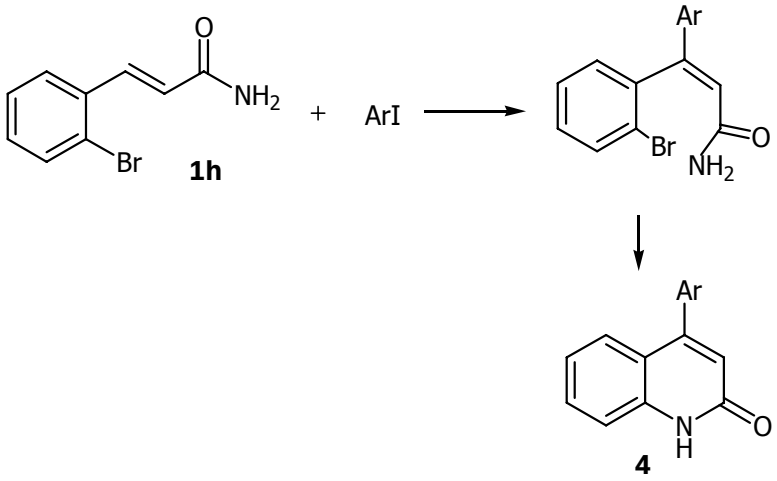


Figure 2

The results obtained with 3-(o-bromophenyl)acrylamide 1f (Table 2, entry 8; Table 3, entry 17) prompted us to investigate the utilization of this chemistry for the prepa-ration of 2-quinolone derivatives, a class of compounds abundant in many biologically active compounds, [11] through a process involving a Heck reaction followed by an intramolecular carbon-nitrogen bond forming step (Scheme 3).

With regard to the cyclization step, the economic attractiveness of copper-based methods and the growing interest in copper-catalyzed syntheses[12] stimulated us to develop a copper-catalyzed protocol.



Scheme3

Using the vinylic substitution product **2h** as the model system, the cyclization reaction was attempted under a variety of reaction conditions. As shown in Table 4, the highest yield was obtained in the presence of 0.2 equiv of CuI, 2 equiv of NaI, [13] 2 equiv of K_3PO_4, 0.4 equiv *N,N*-dimethylethylendiamine (DMEDA) in dioxane at 120 °C. To make this overall approach to 2-quinolones more attractive from a synthetic standpoint, we explored the vinylic substitution and cyclization of **1f** through a process that would omit the isolation of vinylic substitution intermediates. After some experimentation, we were pleased to find that adding CuI, NaI, K_3PO_4, *N,N*-dimethylethylendiamine and dioxane to the crude mixture derived from the Heck reaction after work-up gave quinolone products in good to high overall isolated yields with neutral,

Table 4. Examination of the Copper-Catalyzed Cyclization of **2h** to the Quinolone Product **4b**.[a]

entry	catalyst system	base	additive	ligand	T (°C)	t (h)	**4b** yield %[b,c]
1	$CuCl(PPh_3)$	K_3PO_4	-	-	110	20	50 (-)
-	CuI	K_3PO_4	NaI	1,3-DAP[d]	110	96	50 (50)
3	CuI	K_3PO_4	-	DMEDA	110	48	66 (34)
4	CuI	K_3PO_4	-	DMEDA	120	96	56 (40)
5	CuI	-	NaI	DMEDA	120	48	16 (83)
6	CuI	K_3PO_4	NaI	DMEDA	120	24	85 (-)

[a] All reactions were carried out on a 0.5 mmol scale using 1 equiv of **1h**, 0.2 equiv of the copper catalyst, 2 equiv of NaI (when added), 2 equiv of K_2CO_3 (when added), 0.4 equiv of 1,3-DAP or DMEDA (when added) in 2 mL of dioxane. [b] Yields are given for isolated products.[c] Figures in parentheses refer to the recovered starting material.[d] 1,3-Diaminopropane

Table 5 Synthesis of 4-Aryl-2-quinolones **4** through a Sequential Heck Reaction/Copper-Catalyzed Cyclization of β-(o-Bromophenyl)acrylamide **1h**.

entry	ArI	t (h)		**4** overall yield %[b] (procedure)
		Heck reaction	cyclization	
1	*m*-MeO-C_6H_4-I	48	24	**4a** 71 (A)
2	*p*-MeO-C_6H_4-I	12	24	**4b** 77 (A)
3	Ph-I	48	24	**4c** 77 (A)
4	*m*-F-C_6H_4-I	48	24	**4d** 71 (B)
5	*p*-EtOOC-C_6H_4-I	48	24	**4e** 60 (B)

[a] Reactions were carried out on a 0.5 mmol scale as follows: (procedure A) 1 equiv of **1**, 1.5 equiv of aryl iodide, 3 equiv of Et_3N and 0.05 equiv of $Pd(OAc)_2$ at 100 °C, work-up, and then 0.2 equiv of CuI, 2 equiv of NaI, 2 equiv of K_2CO_3, 0.4 equiv of DMEDA and 2 mL of dioxane at 120 °C; (procedure B) 1 equiv of **1**, 2.5 equiv of aryl iodide, 5 equiv of Et_3N and 0.01 equiv of $Pd(OAc)_2$ at 100 °C, work-up, and then as for procedure A.
[b] Yields are given for isolated products.

electron-rich and electron-poor aryl iodides (Table 5). None of the quinolone derivative was obtained when the vinylic substitution/cyclization protocol was attempted under optimized conditions omitting CuI.

Conclusion

In conclusion, we have shown that the palladium-catalyzed reaction of β-arylacrylamides with aryl iodides in the presence of triethylamine affords vinylic substitution products usually in high yield. The nature of β-substituents, aryl iodides and substituents at the nitrogen atom was found to influence the stereochemical outcome of the reaction. In particular, the presence of β-substituents containing electron-withdrawing groups in the carbopalladation adduct appear to afford higher diastereoselectivity; *N,N*-dimethyl-β-arylacrylamides tend to give a higher diastereoselectivity than the corresponding *N*-unsubstituted β-arylacrylamides; β-arylacrylamides containing *ortho* substituents lead to the formation of only one stereoisomer. The procedure was used to develop an efficient approach to 4-aryl-2-quinolones from β-(*o*-bromophenyl)acrylamide through a sequential Heck reaction/copper-catalyzed cyclization process.

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4-ARYL-2-QUINOLONES THROUGH A PSEUDO-DOMINO HECK/BUCHWALD-HARTWIG REACTION IN A MOLTEN TETRABUTYLAMMONIUM ACETATE/TETRABUTYLAMMONIUM BROMIDE MIXTURE

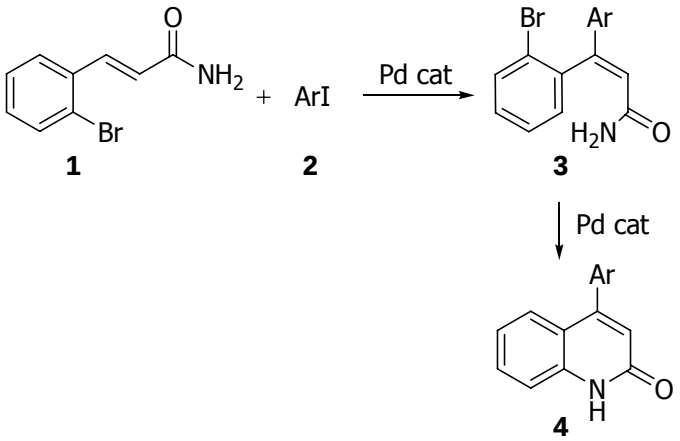
Introduction

The construction of heterocyclic rings based upon the concept of the domino Heck reaction/cyclization process is a useful synthetic methodology.[1] We developed this chemistry into new versatile and efficient procedures for the preparation of butyrolactones,[2] cardenolides,[3] butenolides,[4] quinolines,[5] and coumarins.[5,6] In all these processes, an α,β-unsaturated carbonyl compound bearing a nucleophile on the β substituent undergoes an initial palladium-catalyzed vinylic substitution followed, in some cases in situ, by an intramolecular nucleophilic attack of an oxygen or nitrogen nucleophile to the carbonyl group. Recent developments in the palladium-catalyzed N- and O-arylation process,[7] pioneered and extensively investigated by Buchwald[8] and Hartwig,[9] prompted us to explore a different strategy, in which the Heck reaction of an olefinic system, bearing an *ortho* C-Br bond on the β aryl substituent, could be followed by a palladium-catalyzed $C_{(aryl)}$-heteroatom bond forming reaction in situ.

In particular, we decided to develop a new approach to the de novo 2-quinolone system construction using the readily available 3-(*o*-bromophenyl)acrylamide **1** as the building block according to the domino process[10] outlined in Scheme 1. The initial Heck reaction should produce the vinylic substitution product **3** which, under the same conditions, should undergo an intramolecular palladium-catalyzed N-arylation to give the desired 2-quinolone product **4**.

Though palladium catalysis revealed a powerful tool for the construction of heterocyclic rings, [11] very few examples of palladium-catalyzed synthesis of 2-quinolones have been reported. Internal alkynes have been recently described by Larock et al. [12] to give 2-quinolones via carbonylative annulation by *N*-substituted *o*-iodoanilines. Olefinic systems have also been used as precursors. (*Z*)-2-acetamido-α-bromostyrene was converted into 2-quinolone via a carbonylation/cyclization process.[13] β-Substituted acrylic acid derivatives and methyl acrylate

were used to prepare 2-quinolones through an Heck reaction/cyclization process with, respectively, *o*-iodoanilines[1] and *o*-bromonitrobenzenes.[14] The utility of the olefinic-based methods, however, appears to be severely limited.



Scheme 1

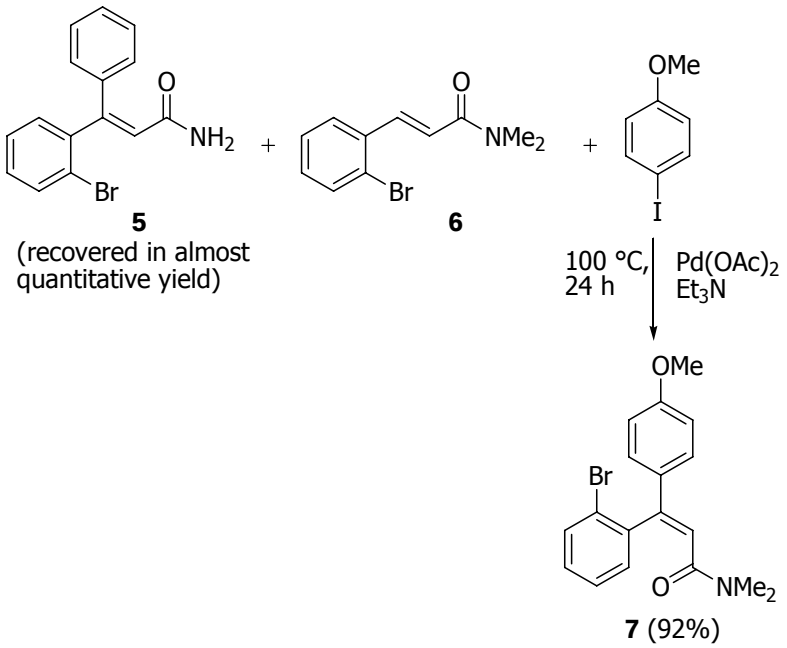
On the other hand, the 2-quinolone motif is abundant in many biologically active compounds and this appears to justify efforts to develop new and versatile synthetic procedures. For example, 2-quinolone derivatives have been evaluated as inhibitors of HIV-1 reverse transcriptase, [15] gonadotropin releasing hormone antagonists,[16] NMDA and AMPA antagonists,[17] antiinfectives,[18] antiviral and antihypertensive agents.[19] The 4-aryl-2-quinolone derivative tipifarnib exhibits anticancer activity. [20,21] 2-Quinolones are also useful synthetic intermediates. For example, they can be readily converted into 2-chloroquinoline derivatives[22] and quinoline-2-triflates[23] and then into 2-amino quinoline derivatives. 2-Chloroquinolines[24] and quinoline-2-triflates[25] can also be involved in palladium-catalyzed reactions to afford a wide range of quinoline products.

Results and discussion

Initial attempts focused on exploring the feasibility of the domino process outlined in Scheme 1. Particularly, we decided to develop reaction conditions in which a single palladium-based catalytic system would share two mechanistically unrelated sequential catalytic cycles.[26,27] The successful execution of this type of domino processes - a palladium-catalyzed pseudo-domino (Pd-PDOM) *type I* process according to the definition given by Poli et al.[26f] - is not a trivial task. Possible and often unpredictable incompatibilities among the different catalytic cycles can in fact make this synthetically useful chemistry not viable. In the present case, it is also necessary to avoid the intermolecular N-arylation of the starting amide, a reaction which might be expected to be competitive. [28a-e] Furthermore, the formation of the *Z* isomer **3** in the Heck reaction is a vital prerequisite for the success of the cyclization step. [29]

p-Iodoanisole and **1** were used as the model system and the following reaction variables were examined: the bases, the additives, the nature of phosphine ligands, and the reaction temperature. Under a variety of conditions typical for the Heck reaction, using 5 mol% of $Pd(OAc)_2$ as the source of Pd(0), Et_3N (3 equiv) as the base, PPh_3 (10 mol %) and DMF as the solvent at 100 °C the starting olefin was recovered in 80-90% yield. The use of the Herrmann catalyst[30] under the same conditions produced the vinylic substitution product **3a** in 58% yield along with minor amounts of **4a** (18%). The starting material was recovered in 18%. Increasing temperature to 120 °C gave **3a** in 38% yield and the starting olefin was recovered in 38% yield. Neither the vinylic substitution derivative nor the quinolone product was formed at 100-120 °C under the conditions developed by Buchwald et al. for the intramolecular aryl amidation[28g] (toluene, MOP[31] or Xantphos, [32] K_2CO_3). Attempts to combine some typical elements of the intramolecular N-arylation of amides with those of the vinylic substitution met with failure. For example, treatment of **1** with 1.5 equiv of *p*-iodoanisole, 2 equiv of Cs_2CO_3, 0.05 equiv of $Pd(OAc)_2$, 0.05 equiv of Xantphos in DMF at 100 °C for 48 h, led to the isolation of **3a** and **4a** in 40 and 11 % yields, respectively. Omitting phosphine ligands led again to the formation of **3a** as the main reaction product under a variety of reaction conditions (Table 1, entries 1-6).

Noteworthy, though formation of *E/Z* mixtures have been reported in previous vinylic substitution reactions of β-substituted acrylamides,[29] only the Heck product containing the amide group on the same side of the carbon-carbon double bond as the preexisting β-substituent was formed, most probably as the result of a diastereoselective Heck reaction. The involvement of an *E/Z* equilibrium following the syn-β-elimination step was ruled out on the basis of the following experiment. A pure sample of **5** (the stereoisomer of **3a**), prepared via the reaction of cinnamamide with *o*-iodobromobenzene, was subjected to the best conditions producing vinylic substitution products (Table 1, entry 6) in the presence of **6** (the *N,N*-dimethyl derivative was used to make it easier the separation of the reaction mixture) and *p*-iodoanisole (Scheme 2). The 3,3-diarylacrylamide **7**, formed via the reaction of **6** with *p*-iodoanisole, was isolated in 92% yield. Compound **5** was recovered in almost quantitative yield and its stereochemistry was maintained, even prolonging the reaction time to 24 h.



Scheme 2

Only after switching to *n*-Bu_4NOAc as the base in DMF at 120 °C did the mixture contain predominantly the desired **4a** (Table 1, entry 7). Though the yield was unsatisfactory from a synthetic standpoint, the very high selectivity in favor of the intramolecular C-N bond forming reaction compared with the intermolecular reaction was rewarding. Indeed, formation of the N-arylation product generated via intermolecular palladium-catalyzed reaction of the amide group of **1** with *p*-iodoanisole, expected as a possible side-reaction, was observed only in trace amounts. We next explored the use of a molten *n*-Bu_4NOAc/*n*-Bu_4NBr mixture as the reaction medium. This molten salt mixture was recently shown by us to be particularly suited for performing highly stereoselective Heck reactions on cinnamate esters[33] and domino Heck reaction/cyclization processes producing coumarins.[6] Initial attempts were discouraging since **3a** was still the main reaction product (Table 1, entry 8). However, the reaction outcome was found to depend on the *n*-Bu_4NOAc/*n*-Bu_4NBr molar ratio and, after some experimentation (the results of a couple of the runs we carried out are shown in Table 1, entries 9 and 10), we arrived at the optimal combination (3 equiv of *n*-Bu_4NOAc and 3 equiv of *n*-Bu_4NBr) which produced **4a** in 73% yield (Table 1, entry 11).This result is particularly interesting because phosphine ligands are known to play a pivotal role in Buchwald-Hartwig N-arylation of amides[28] and, to the best of our knowledge, no examples of this type of chemistry have been reported so far with phosphine-free palladium catalysts. Most probably, under our conditions the reaction involves tetraalkylammonium-stabilized palladium nanoparticles[34] and this may have an influence on the reaction outcome. The intramolecular nature of the C-N bond forming process must also favor the reaction.

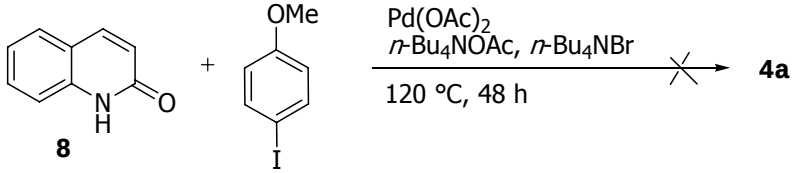
No evidence of the vinylic substitution intermediate **3a** was attained by monitoring the reaction mixture by TLC or HPLC. However, subjecting a pure sample of **3a** to the conditions shown in Table 1, entry 11 produced **4a** in 80% yield (no starting material was detected by HPLC when we monitored the reaction mixture after 45 min). In addition, the reaction under the same conditions of *p*-iodoanisole with the parent quinolone **8** - which might form via an *E/Z* isomerization of **1** followed by a cyclization step - did not afford the quinolone derivative **4a**[35] (Scheme 3). Compound **8** was recovered in almost quantitative yield. Taken together, these

results support the view that **3a** is the precursor of **4a** and that a fast cyclization step follows the Heck reaction under these conditions.

Table 1. Bases, Additives and Temperature in the Palladium-Catalyzed Synthesis of **4a** from **1** and *p*-Iodoanisole.[a]

entry	reaction conditions	°C/h	yield % of **3a**[b]	yield % of **4a**[b]
1	DMF,[c] Et_3N (3 eq.)	100/48	56	-
2	DMF,[c] Et_3N (3 eq.), LiCl (5 eq.)	100/48	46	-
3	DMF,[c] Cs_2CO_3 (2 eq.), LiCl (5 eq.)	100/48	40	-
4	DMF,[c] Na_2CO_3 (2 eq.), LiCl (5 eq.)	100/48	40	-
5	DMF,[c] *n*-Bu_4NOAc (2 eq.)	100/48	53	22
6	Et_3N (5 eq.)	100/12	87	-
7	DMF,[c] *n*-Bu_4NOAc (2 eq.)	120/48	12	33
8	*n*-Bu_4NOAc (1 eq.)	120/48	50	25
9	*n*-Bu_4NOAc (2 eq.) *n*-Bu_4NBr (2 eq.)	120/48	35	35
10	*n*-Bu_4NOAc (2.5 eq.) *n*-Bu_4NBr (4 eq.)	120/48	23	52
11	*n*-Bu_4NOAc (3 eq.) *n*-Bu_4NBr (3 eq.)	120/48	-	73

[a] Reactions were carried out on a 0.5 mmol scale under argon using 1 equiv of **1**, 1.5 equiv of *p*-iodoanisole, and 0.05 equiv of $Pd(OAc)_2$. [b]Yields are given for isolated products. [c] 2 mL.

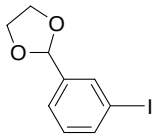
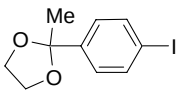


8

Scheme 3

We have also repeated the experiment described in Scheme 2 using the reaction conditions shown in Table 1 entry 11. The 3,3-diarylacrylamide 7 was isolated in 87% yield, compound 5 was recovered in 70% yield and quinolone 4n was obtained in 15% yield (no evidence of its stereoisomer 3a was attained). This result suggests that under these conditions an *E/Z* isomerization process might follow the vinylic substitution step.

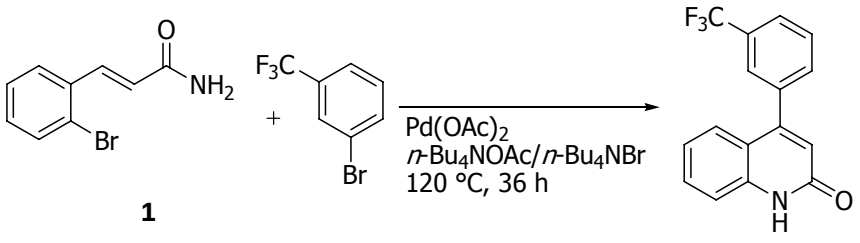
Table 2. Synthesis of 2-Quinolones **4** through a Domino Heck/Buchwald-Hartwig Process.[a]

entry	aryl iodide **2**		t (h)	yield % of **4**[b]	
1	*p*-MeO-C_6H_4-I	**2a**	24	73	**4a**
2	*p*-Me-C_6H_4-I	**2b**	36	65	**4b**
3	*m*-MeO-C_6H_4-I	**2c**	36	65	**4c**
4	*m*-F-C_6H_4-I	**2d**	36	62	**4d**
5	*m*-CF_3-C_6H_4-I	**2e**	36	50	**4e**
6	*p*-CO_2Et-C_6H_4-I	**2f**	36	40	**4f**
7	*o*-F-C_6H_4-I	**2g**	48	40	**4g**
8	*m*-HCO-C_6H_4-I	**2h**	48	20[c]	**4h**
9		**2i**	24	60	**4i**
10	*p*-MeCO-C_6H_4-I	**2j**	48	-	**4j**
11		**2k**	24	80	**4k**
12	*p*-MeCON(Me)-C_6H_4-I	**2l**	48	65	**4l**
13	*m*-MeCON(Me)-C_6H_4-I	**2m**	48	54	**4m**
14	PhI	**2n**	24	75	**4n**

[a]Unless otherwise stated, reactions were carried out on a 0.5 mmol scale at 120 °C under argon using 1 equiv of **1**, 1.5 equiv of **2**, 3 equiv of *n*-Bu_4NOAc, 3 equiv of *n*-Bu_4NBr and 0.05 equiv of $Pd(OAc)_2$. [b]Yields are given for isolated products. [c] Calculated by NMR analysis

The best conditions found with the model reaction [*n*-Bu_4NOAc (3 equiv), *n*-Bu_4NBr (3 equiv), $Pd(OAc)_2$ (0.05 equiv), 120 °C] were then used when the pseudo-domino reaction was extended to other aryl iodides in order to examine the scope and limitations of this process. The results are summarized in Table 2. 4-Aryl-2-quinolones were isolated in allowable to good yields in any cases with a variety of aryl iodides including ether, amide, and ester functionalities. Unfortunately, *m*-iodobenzaldehyde gave the corresponding 2-quinolone product in low yield (Table 2, entries 8) and when *p*-iodoacetophenone was subjected to our standard conditions the corresponding quinolone derivative was not obtained at all (Table 2, entry 10). However, appropriately protected aldehydic and ketonic aryl iodides afforded the desired products in good to high yield. (Table 2, entries 9 and 11).

Attempts to extend the reaction to aryl bromides were also made. However, aryl bromides such as *N.N*-dimethyl-*p*-bromoaniline, *p*-bromoanisole, *o*-fluorobromobenzene, and *p*-bromobenzonitrile failed to give quinolone products, generating complex reaction mixtures we have not further investigated. Very likely, oxidative addition of the aryl bromide fragment of **1** to Pd(0) may be a significant competitive reaction in these cases. Nevertheless, *m*-trifluoromethylbromobenzene produced the corresponding 2-quinolone derivative in satisfactory yield (Scheme 4), comparable to that obtained with *m*-trifluoromethyliodobenzene (Table 2, entry 5).



1

48%

Scheme 4

Conclusion

We have developed a straightforward new approach to 4-aryl-2-quinolones from readily available starting materials using $Pd(OAc)_2$ as the precatalyst and a molten *n*-Bu_4NOAc/*n*-Bu_4NBr mixture as the reaction medium. The phosphine-free catalyst system works well even in the intramolecular C-N bond forming step. Although isolated yields are moderate to good, they refer to a multistep palladium-catalyzed pseudo-domino process involving two mechanistically independent, sequential catalytic cycles. On the whole, the present procedure may represent a convenient alternative to known olefinic-based[1,13,14] palladium-catalyzed syntheses of this class of compounds.

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PALLADIUM-CATALYZED SYNTHESIS OF LIPOPHILIC BENZO[*b*]FURANS FROM CARDANOL

Introduction

Because of their occurrence in a wide variety of natural substances and biologically active compounds, benzo[*b*]furans are privileged substructures [1] of considerable importance. For example, benzo[*b*]furan derivatives have been investigated as antagonists of the angiotensin II receptor,[2] antitumoral agents, [3] calcium entry blockers, [4] inhibitors of 5-lipoxygenase,[5] of the blood coagulation factor Xa [6] and of the E-selectin-mediated cell adhesion, [7] ligands of adenosine A_1 receptor[8] and modulators of vitamin D receptor.[9] Some of them have shown antiarrhythmic activity,[10] antioxidant activity, [11] and can be used in the treatment of 5-HT6 receptor-related disorders.[12] Studies have also been performed to evaluate the influence of lipophilicity on their activities. [13]

In this last context, as part of ongoing program concerning the utilization of renewable organic material as starting materials to obtain new compounds of biological interest, [14] we decided to use cardanol, a natural phenolic lipid readily obtained by vacuum distillation of cashew nut shell liquid (CNSL), as precursor for the construction of lipophilic benzo[b]furans derivatives via palladium-catalyzed cyclization of acetilenic building block. [15]

Cashew nut shell liquid (CNSL) is the by-product of the cashew tree (*Anacardium occidentale L.)* industry. [16] Chemically, it is mainly constituted from 3-*n*-pentadecyl-phenol (cardanol) and its derivatives with insaturation on the alkylic chain. The latter could be easily reconverted in 3-*n*-pentadecyl-phenol by simple catalytic hydrogenation. In smaller amount there are cardol, methylcardol and anacardic acid (Figure 1). CNSL is a cheap and renewable substance which can be employed for making of a multitude of useful products; in fact it is widely employed in more fields of manufacture of resins and plastics, surface coatings, adhesives, laminates, rubber compounding. Greater utilization of CNSL for industrial polymer products can be an attractive proposal in view of its low cost, abundant availability and chemically reactive nature.

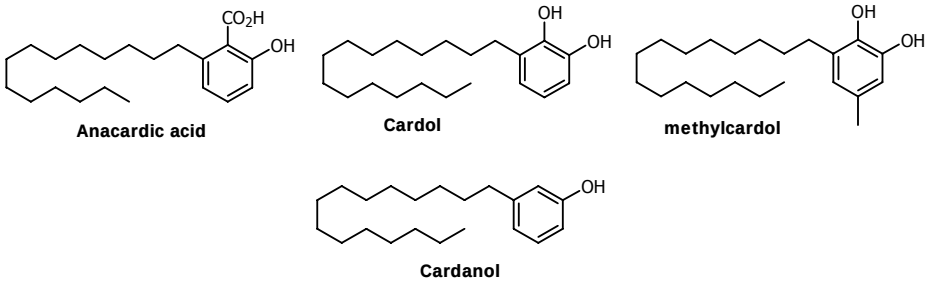
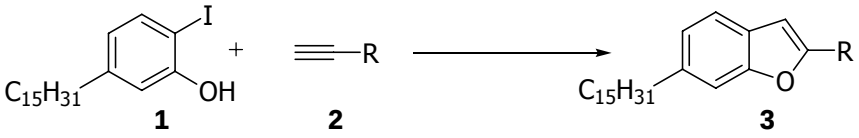


Figure 1

Results and discussion

Cardanol was initially converted into *o*-iodocardanol 1 in 55-60% yield via iodination with I_2 in the presence of H_2O_2 at 50°C.[17] Minor amounts of *o,p*-diiodocardanol were also obtained. Then, we explored the preparation of 2-substituted benzo[*b*]furans from **1** via a Sonogashira cross-coupling/cyclization process with terminal alkynes (Scheme 1).

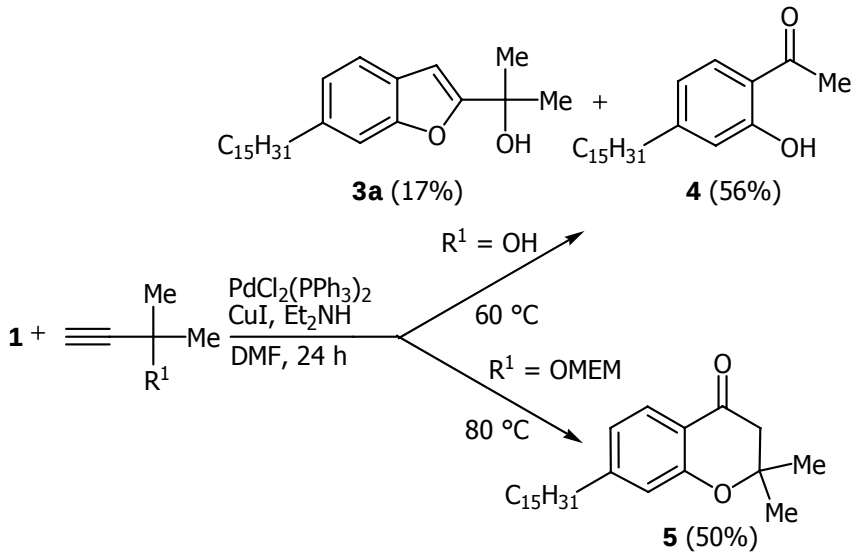


Scheme 1

Initial attempts were made using conditions similar to those we employed in our previous work on benzofuran synthesis,[15a] in which cyclization products were formed under cross-coupling conditions through a domino process. However, in contrast to the general trend of *o*-iodophenols and terminal alkynes,[15c] *o*-iodocardanol was found to exhibit an unusual reactivity.[18] When 3-butyn-2-methyl-2-ol and *o*-iodocardanol, our model system, were treated with 0.02 equiv of $PdCl_2(PPh_3)_2$, 0.04 equiv of CuI and 2 equiv of Et_2NH in DMF at 60 °C for 24 h, the benzo[*b*]furan derivative **3a** was isolated in low yield. The main product was the acetophenone derivative **4** (Scheme 2), most probably derived from the initially formed cross-

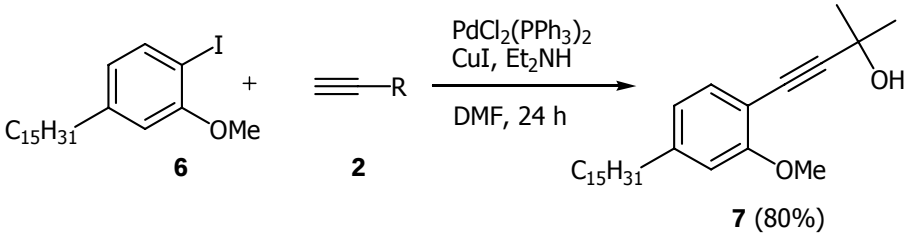
coupling intermediate via regioselective addition of water to the carbon-carbon triple bond followed by removal of the alcoholic group as acetone through a retroaldolic reaction.

The utilization of the MEM derivative of 3-butyn-2-methyl-2-ol to avoid the removal of the alcoholic group resulted in the formation of the chroman-4-one **5** (50% yield), possibly via Sonogashira cross-coupling, addition of water to the carbon-carbon triple bond, an elimination step, and conjugate addition of the phenolic oxygen to the resultant α,β-unsaturated carbonyl compound (Scheme 2). Apparently, the addition of water to the C-C triple bond of the coupling intermediate in these cases is faster than the desired intramolecular cyclization onto the phenolic oxygen. The reason of this behavior is not yet understood and is not further commented herein. However, it is worth noting that, to the best of our knowledge, the formation of ketones via domino Sonogashira cross-coupling/addition of water has never been reported in the numerous applications of the palladium-catalyzed synthesis of benzo[*b*]furans from terminal alkynes and *o*-iodophenols described in literature [15c] and even in the Sonogashira cross-couplings conducted in aqueous media. [19]



Scheme 2

Though we have not investigated the details of this transformation, we found that the formation of the ketonic derivative depends on the presence of the free phenolic oxygen. Indeed, when the Sonogashira cross-coupling was carried out under usual conditions using the methyl derivative **6**, the cross-coupling product **7** was isolated in 80% yield and no evidence of the corresponding ketonic product was attained (Scheme 3).

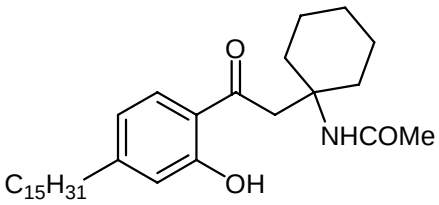


6 **2** **7** (80%)

Scheme 3

After some experimentation, benzo[*b*]furan **3a** was isolated in 65% yield from *o*-iodocardanol and 3-butyn-2-methyl-2-ol by running the Sonogashira cross-coupling at 60 °C [0.02 equiv of $PdCl_2(PPh_3)_2$, 0.04 equiv of CuI, 2 equiv of Et_2NH, DMF] till the disappearance of *o*-iodocardanol and then increasing the temperature to 80 °C to form the cyclization derivative. Under these conditions, a variety of other 2-substituted benzo[*b*]furans were prepared in good to excellent yields (Table 1, entries 1-11, 14).

Only *N*-(1-ethynylcyclohexyl)-acetamide, among the substrates we tested, gave the desired benzo[*b*]furan product in low yield, the main product being the ketone derivative **8** (Figure 2) isolated in 60% yield (Table 1, entry 13).

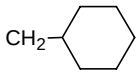
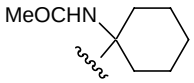
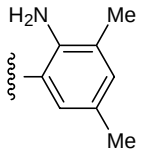


8

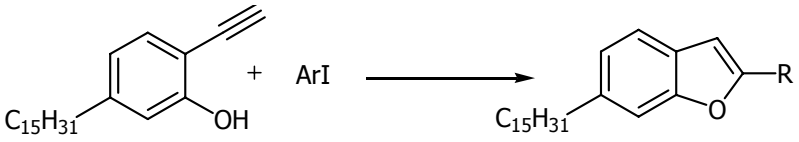
Figure 2

With phenylacetylene the benzo[*b*]furan derivative was isolated in excellent yield warming the reaction mixture directly to 80 °C (Table 1, entry 12).

Table 1. Preparation of 2-Substituted Benzo[*b*]furans **3** via Palladium-Catalyzed Reaction of *o*-Iodocardanol **1** with Terminal Alkynes **2**.[a]

entry	1-alkyne 2 R	T (°C)/t (h)	T (°C)/t (h)	yield % of **3**[b]	
1	$C(OH)Me_2$	60/1	80/3	65	**3a**
2	CH_2CH_2Ph	60/24	80/12	83	**3b**
3		60/7	80/17	56	**3c**
4	C_6H_4-*o*-OMe	60/24	80/12	65	**3d**
5	C_6H_4-*m*-OMe	60/0.5	80/5	70	**3e**
6	C_6H_4-*p*-CH_2OH	60/1	80/4	55	**3f**
7	C_6H_4-*p*-NHCOMe	60/0.5	80/5	87	**3g**
8	C_6H_4-3-NO_2-4-Me	80/26	-	62	**3h**
9	C_6H_4-*p*-CO_2Me	60/4	80/20	60	**3i**
10	C_6H_4-*p*-Cl	60/2	80/22	75	**3j**
11	C_6H_4-*p*-COMe	60/4	80/20	55	**3k**
12	Ph	80/5	-	95	**3l**
13		60/1	80/4	23[c]	**3m**
14		60(1)	80(4)	60	**3n**

[a] Reactions were carried out on a 0.20-0.23 mmol scale under argon using 1 equiv. of 1, 1.5 equiv. of 2, 0.02 equiv. of $PdCl_2(PPh_3)_2$, 0.04 equiv. of CuI, 0.3 mL of Et_2NH, and 0.2 mL of DMF.
[b] Yields are given for isolated products.
[c] The ketone derivative 6 was isolated in 60% yield



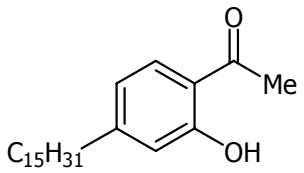
9 **10** **3**

Scheme 4

The preparation of **3** from *o*-iodocardanol **1** and terminal alkynes **2** described above requires a specific acetylenic building block for each benzo[*b*]furan. This may sometimes limit the synthetic scope of the procedure. Therefore, we decided to explore an alternative preparation in which 2-substituted benzo[*b*]furans are synthesized from the same acetylenic building block: *o*-ethynylcardanol **9** (Scheme 4).

o-Ethynylcardanol **9** was best prepared (60% overall isolated yield) from *o*-iodocardanol via Sonogashira reaction with trimethylsilylacetylene [20] followed by desilylation of the isolated cross-coupling derivative. Even in this case *o*-iodocardanol showed a different reactivity compared with a variety of other *o*-iodophenols, whose cross-coupling derivatives can usually be desilylated through a one-flask process, omitting their isolation.[15b]

o-Ethynylcardanol **9** and iodobenzene were used as the model system. Initially, the coupling/cyclization process to the corresponding 2-phenylbenzo[*b*]furan was carried out using 1.5 equiv. of **9**, 1 equiv. of iodobenzene, 0.02 equiv of $PdCl_2(PPh_3)_2$, 0.04 equiv. of CuI, 0.3 mL of Et_2NH, and 0.2 mL of DMF (Table 2). At room temperature as well as at 40 °C (entries 1 and 2) ketone 11 was obtained as the main product. Increasing the reaction temperature to 60 °C led to the isolation of 2-phenylbenzo[*b*]furan 3l in 30% yield along with a 40% yield of **11**(Figure 3).



11

Figure 3

Table 2. Temperature and Molar Ratios in the Cross-Coupling/Cyclization of *o*-Ethynylcardanol **9** with Iodobenzene.

entry	temperature (°C)	time (h)	yield % of **3l**[a]	yield % of **11**[a]
1	r.t.	24	–[b,c]	40
2	40	24	–[b,c]	30
3	60	24	30[b,c]	40
4	60	8	75[b,d]	–

[a] Yields are given for isolated products.
[b] Reactions were carried out on a 0.16 mmol scale under argon using 0.02 equiv. of $PdCl_2(PPh_3)_2$, 0.04 equiv. of CuI, 0.3 mL of Et_2NH, and 0.2 mL of DMF.
[c] In the presence of 1.5 equiv. of **9** and 1 equiv. of iodobenzene,
[d] In the presence of 1 equiv. of **9** and 1.5 equiv of iodobenzene.

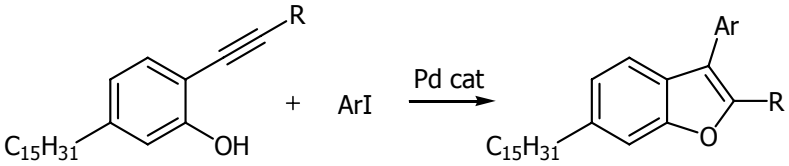
Using 1 equiv of **9** and 1.5 equiv of iodobenzene at 60 °C and maintaining all the other parameters the same we were able to isolate **3l** in 75% yield (entry 4). Under these conditions other aryl iodides were converted into the corresponding 2-substituted benzo[*b*]furans in good yields (Table 3).

Table 3. Cross-Coupling/Cyclization of *o*-Ethynylcardanol **9** with Aryl Iodides **10**.[a]

entry	aryl iodided	time (h)	yield % of **3**[b]	
1	PhI	8	75	**3l**
2	*p*-MeO-C_6H_4-I	8	70	**3o**
3	*m*-F-C_6H_4-I	24	70	**3p**
4	*m*-CF_3-C_6H_4-I	24	65	**3q**

[a] Reactions were carried out on a 0.16 mmol scale under argon using 1 equiv. of **9**, 1.5 equiv. of **10**, 0.02 equiv. of $PdCl_2(PPh_3)_2$, 0.04 equiv. of CuI, 0.3 mL of Et_2NH, and 0.2 mL of DMF.
[b] Yields are given for isolated products.

In order to achieve a higher degree of functionalization, we next attempted the preparation of 2,3-disubstituted benzo[*b*]furans **13** from *o*-alkynylcardanols **12** through our oxypalladation-reductive elimination process (Scheme 5).[15b]



12 **10** **13**

Scheme 5

The starting *o*-alkynylcardanols **12** were prepared through Sonogashira cross-coupling of *o*-iodocardanol **1** with terminal alkynes according to the conditions described previously.[16b] *o*-(Phenylethynyl)cardanol **12a** and iodobenzene were initially selected as the model system. The influence of bases, solvents, catalyst systems, and temperature were briefly investigated and some results from our optimization work are summarized in Table 4.

Table 4. Solvents, Catalyst Systems and Temperature in the Palladium-Catalyzed Reaction of **12a** with Iodobenzene.

entry	Pd	ligand	base	solvent	temperature (°C)	Time (h)	Yield % **13a**[c]	Yield % **3a**[c]	Yield % **12a**[c] recovered
1[a]	$Pd(PPh_3)_2$	–	Cs_2CO_3	toluene	50	48	–	20	50
2[a]	$Pd(PPh_3)_2$	–	K_2CO_3	MeCN	50	48	51	38	–
3[a]	$Pd(PPh_3)_2$	–	K_2CO_3	MeCN	60	48	34	27	–
4[c]	$Pd_2(dba)_3$	bpy	K_2CO_3	MeCN	50	5	75	–	–

[a] Carried out on a 0.16 mmol scale under argon using 1 equiv of **12a**, 1.5 equiv of iodobenzene, 0.05 equiv. of $Pd(PPh_3)_2$, 2 equiv of carbonate base and 0.5 mL of solvent.
[b] Yields are given for isolated products.
[c] Carried out on a 0.16 mmol scale under argon using 1 equiv. of **12a**, 2 equiv. of iodobenzene, 0.05 equiv. of $Pd_2(dba)_3$, 0.1 equiv. of bpy, and 0.5 mL of MeCN.

A variety of conditions proved unsuccessful since the direct cyclization to **3a** was found to be predominant (Table 4, entry 1) or a significant side reaction (Table 4, entries 2 and 3). The use of bipyridine (bpy) as ligand [17] gave the best results leading to the formation of **12a** in high yield (Table 4, entry 4)

These conditions were used when the process was extended to include other *o*-alkynylcardanols and aryl iodides. The results of this study are summarized in Table 5.

Table 5. Synthesis of 2,3-Disubstituted Benzo[*b*]furans **13** from *o*-Alkynylcardanols **12** and Aryl Iodides **10**.[a]

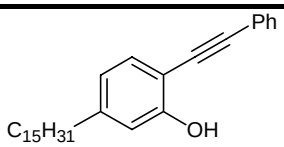
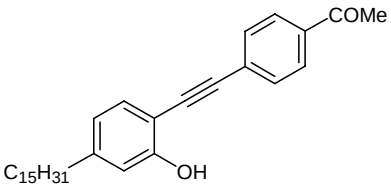
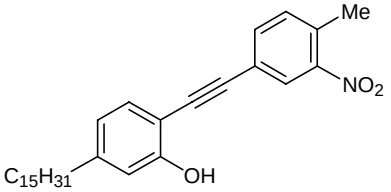
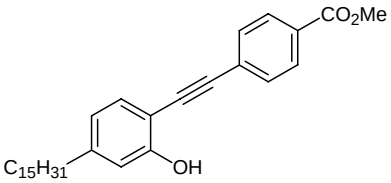
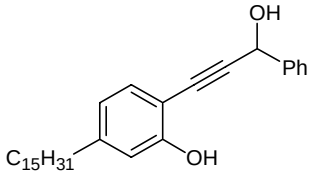
.entry	*o*-alkynylcardanol **12**		aryl iodide **10**	time (h)	yield % of **13**[b]	
1		**12a**	PhI	5	70	**13a**
2		**12a**	*p*-MeO-C_6H_4-I	5	75	**13b**
3		**12a**	*p*-MeCO-C_6H_4-I	5	90	**13c**
4		**12b**	PhI	5	75	**13d**
5		**12c**	PhI	24	65[c]	**13e**
6		**12c**	*p*-MeO-C_6H_4-I	24	60[d]	**13f**
7		**12c**	*p*-MeCO-C_6H_4-I	36	40[e]	**13g**
8		**12d**	PhI	8	75	**13h**
9		**12d**	*p*-MeO-C_6H_4-I	8	80	**13i**
10		**12d**	*p*-MeCO-C_6H_4-I	24	77	**13j**

Table 5 (continue). Synthesis of 2,3-Disubstituted Benzo[*b*]furans **13** from *o*-Alkynylcardanols **12** and Aryl Iodides **10**.[a](Continue)

entry	*o*-alkynylcardanol **12**		aryl iodide **10**	time (h)	yield % of **13**[b]	
11		**12e**	PhI	24	60	**13k**
12		**12e**	*p*-MeO-C_6H_4-I	24	65	**13l**
13		**12e**	*p*-MeCO-C_6H_4-I	24	50	**13m**

[a] Reactions were carried out on a 0.12-0.15 mmol scale at 50 °C under argon using 1 equiv. of **12**, 2 equiv. of **10**, 0.05 equiv. of $Pd_2(dba)_3$, 0.1 equiv. of bpy, and 0.5 mL of MeCN.
[b] Yields are given for isolated compounds.
[c] Compound **3h** was isolated in 15% yield.
[d] Compound **3h** was isolated in 15% yield.
[e] Compound **3h** was isolated in 20% yield.

Conclusion

In conclusion, a versatile efficient route to the preparation of lipophilic 2-substituted and 2,3-disubstituted benzo[*b*]furans from a series of readily available cardanol derivatives: *o*-iodocardanol **1**, *o*-ethynylcardanol **9** and *o*-alkynylcardanols **12** has been developed. The effectiveness of our approach to the preparation of this class of compounds is demonstrated by the simplicity of the experimental protocols, the variety of tolerated substituents, and the good to high yields usually observed.

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NEW ARYLATED CATECHINS BY SUZUKI REACTION

Introduction

Agricultural by-products contain a variety of biologically active species which mostly go to waste and are rich in antioxidant polyphenols. For example, the grape pomace consisting of skins, seeds and stems is a rich source of these compounds, particularly in flavan-3-ols (catechins).[1] This group of flavonoids includes catechin, epicatechin, epicatechin gallate (ECG) and epigallocatechin-3-gallate (FGCG) (Figure 1).

Catechins and proanthocyanidins can be recovered by extraction from grape seeds obtained as by-products from wineries, [2] so they are raw materials derived from wastes that can be converted into valuable chemicals.

Catechin, epicatechin and epicatechin gallate play an important role for the human health.[3] In recent years, they have been used as natural antioxidant in oils and fats against lipid oxidation, supplement for animal feeds, antimicrobial agent in foodstuffs and as functional ingredient in various foods and dietary supplements. It was reported that catechin has hydroxyl peroxyl, superoxide and DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging activities and that it can chelate iron. It was found that ECG, epicatechin and catechin have a peroxyl radical scavenging activity ten times higher than L-ascorbate and β-carotene when tested on bacteria. Epicatechin along with catechin have the same activities. [4]

Catechins have been reported to alleviate a number of clinical conditions, like stroke and cerebral haemorrhage cardiovascular and liver diseases bacterial infections and stomach ulcers. Moreover, they may have benefit with regard to the treatment of various allergic disorders and the inhibition of inflammation owing to these beneficial biological activities recently the number of studies and patents about their pharmacological activities is increased particularly in relation to antimicrobial anti-arthritic and anticancer activities. [5]

In order to achieve structure-activity relationships, several synthetic derivatives of catechins have been compared, [6] but only few papers describing the synthesis of new catechin derivatives have been reported [7] as well as their oxidative modification.[8] In particular, the

preparation of catechins less soluble in water to improve absorbtion into living bodies is a subject of great current interest.[9] Therefore, we decided to develop a new synthesis of arylated catechins as shown in Scheme 1.

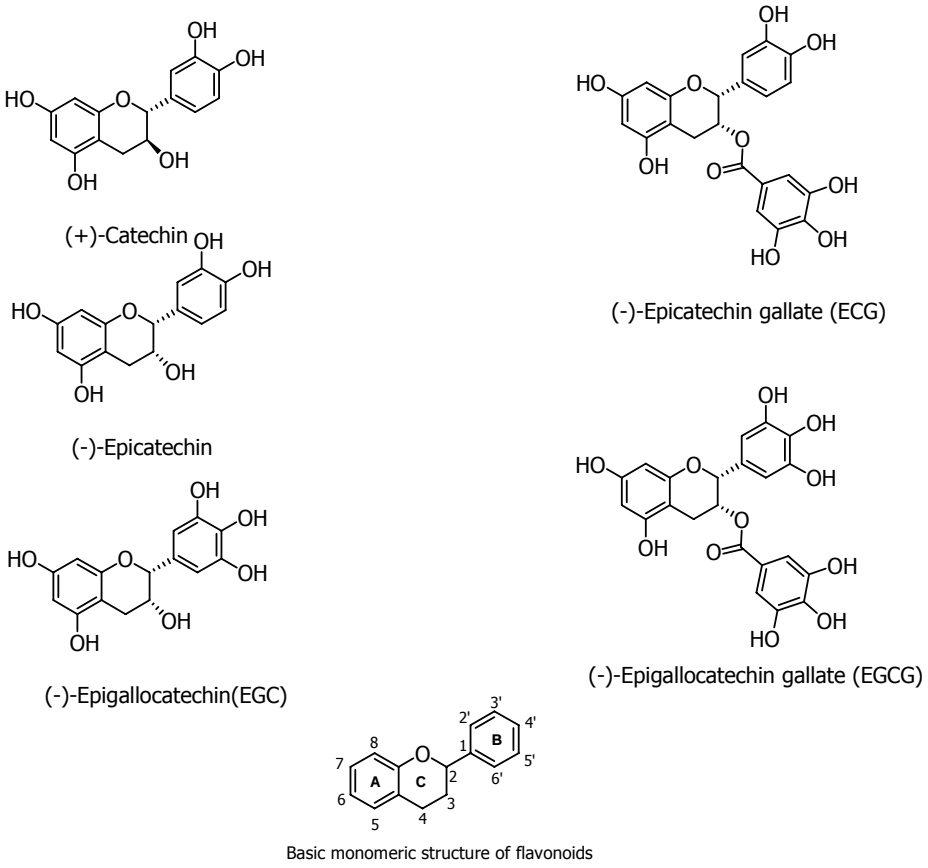
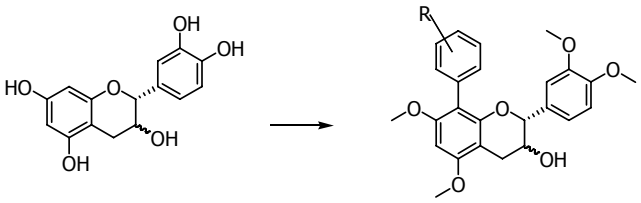


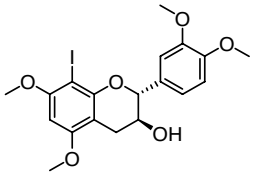
Figure 1



1 **4**

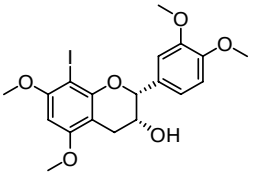
Scheme 1

Surprisingly, despite the remarkable vesatility and efficiency of palladium catalysis in organic synthesis and even in the synthesis and derivatization of heterocyclic compounds, palladium-catalyzed reactions have been rarely mentioned in this area.[10] Therefore, we decided to apply the Suzuki reaction to 8-iodo-catechin-5,7,3',4'-tetramethyl ether **3a** and 8-iodo-epicatechin-tetra-methyl ether **3b** (Scheme 2) to obtain catechin derivatives **4 .** (Scheme 3)



8-iodo-catechin-5,7,3',4'-tetramethyl ether

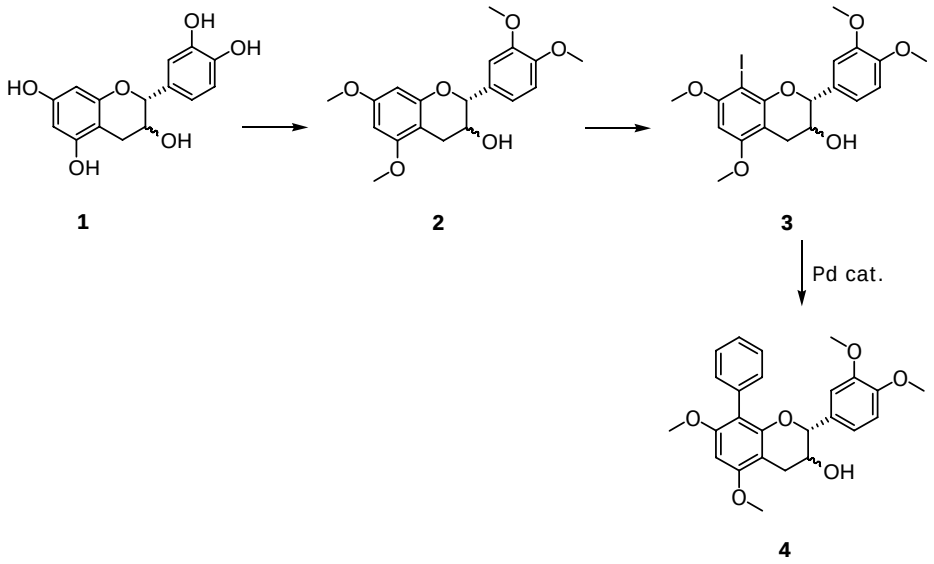
3a



8-iodo-epicatechin-5,7,3',4'-tetra-methyl ether

3b

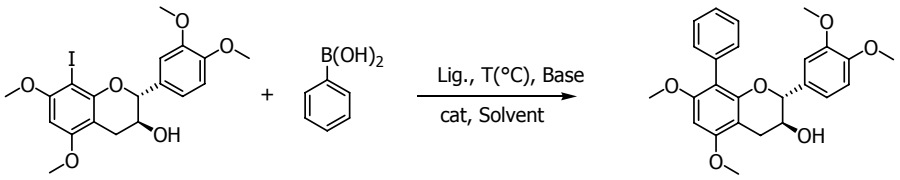
Scheme 2



Scheme 3

Results and discussion

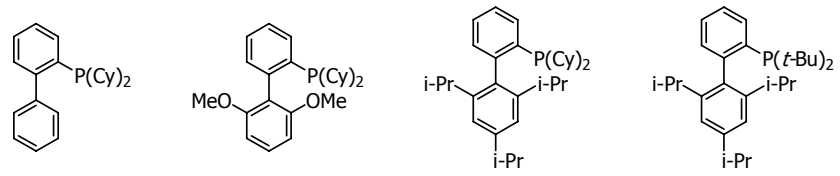
Catechin and epicatechin have been converted into **3a** and **3b** using K_2CO_3 and Me_2SO_4 for the methylation step and NIS in acetone for the iodination of the resultant methyl ethers.[11] Our initial arylation attempts focused on achieving optimal conditions for the reaction of catechin **3a** and phenyl boronic acid**,** selected as the model system. The following reaction variables were examined: the nature of phosphine ligands, bases, solvents, temperature and additives (scheme 4). The results of our screening are summarized in Table 1. One of the most commonly used catalytic system for this type of reaction reaction gave unsatisfactory results (Table 1, entries 7 and 9). Even the use of $(^t\text{But})_3\text{P}$, added as salt to the reaction mixture (Table 1, entry 5), and 2-(2′,4′,6-triisopropylbiphenyl)di^{t}Butilphosphine (Table 1, entry 6) met with failure. Steric hindrance may account for these results.



3a **4**

Scheme 4

We then turned our attention to the utilization of biaryl monophosphines (figure 2), a class of phosphine ligands introduced by Buchwald et al.[12] which were shown to give good results in Suzuki-Miyaura coupling with aryl chlorides.



a **b** **S-phos** **c** **X-phos** **d**

Figure 2

Table 1. Ligands, Pd Catalyst, Solvent, and Temperature Effects in the Reaction of Phenylboronic Acid with 8-Iodo-5,7,3′,4′-catechin Tetramethyl Ether **3a**

entry	Pd	ligand	Add	solvent	T (°C)	Time (h)	Yield % 4	Yield % 3a
1 [a]	$Pd_2(dba)_3$ 0.025 equ.	**c** 0.1 equ.	KF	dioxane	100	48	48	32
2 [a]	$Pd_2(dba)_3$ 0.025 equ.	**a** 0.1 equ.	-	dioxane	80	24	45	44
3 [a]	$Pd_2(dba)_3$ 0.025 equ.	**a** 0.1 equ.	-	dioxane	100	24	31	42
4 [a]	$Pd_2(dba)_3$ 0.025 equ.	**c** 0.1 equ.	-	dioxane	80	24	23	-

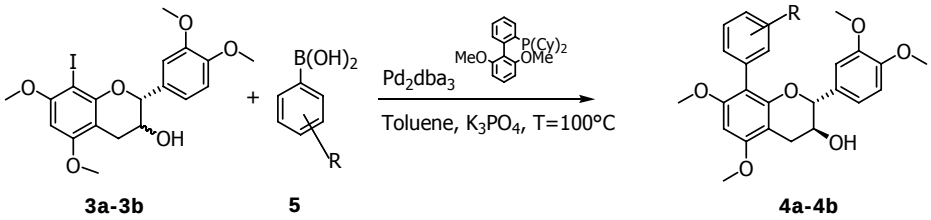
[a] Reactions were carried out on a 0.10 mmol scale under argon using 1 equiv. of 3a,3b 1.5 equiv. of boronic acid 0.7 mL of solvent, and 3 equiv. of K_3PO_4..

Table 1(continue). Ligands, Pd Catalyst, Solvent, and Temperature Effects in the Reaction of Phenylboronic Acid with 8-Iodo-5,7,3′,4′-catechin Tetramethyl Ether **3a**

entry	Pd	ligand	Add	solvent	T (°C)	Time (h)	Yield % 4	Yield % 3a
5 [a]	$Pd_2(dba)_3$ 0.02 equ.	$[(^tBut)_3PH]BF_4$ 0.1 equ.	-	dioxane	60	30	10	60
6 [a]	$Pd_2(dba)_3$ 0.025 equ.	**d** 0.1 equ.	-	dioxane	80	24	-	84
7 [a]	$Pd(PPh_3)_4$ 0.05 equ.	-	-	dioxane	80	24	-	80
8 [a]	$Pd_2(dba)_3$ 0.02 equ.	**b** 0.04 equ.	-	dioxane	100	24	42	-
9 [a]	$Pd_2(dba)_3$ 0.04 equ.	Trifenilfosfina 0.16 equ.	-	Toluene	100	24	-	32
10 [a]	$Pd_2(dba)_3$ 0.02 equ.	**b** 0.04 equ.	-	Toluene	100	5	95	-

[a] Reactions were carried out on a 0.10 mmol scale under argon using 1 equiv. of 3a,3b 1.5 equiv. of boronic acid 0.7 mL of solvent, and 3 equiv. of K_3PO_4..

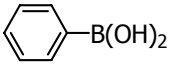
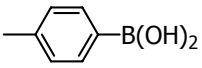
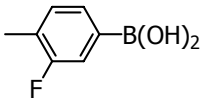
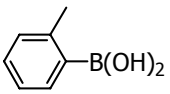
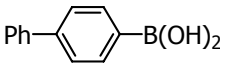
Using 2-(biphenyl)-dicycloexylphosphine (**a**) at 80-100°C (Table 1, entries 2, 3) the desired product **4** was isolated in 44% and 42% yield. Switching to Xphos (**c**) at 80-100°C (Table 1, entries 4, 1) afforded results comparable with 2-(biphenyl)-dicycloexylphosphine. Using $Pd_2(dba)_3$ and Sphos (**b**) produced compound **4** in 42% yield in dioxane and 95% in toluene. The latter conditions were consequently applied to a variety of other aryl boronic acids with catechin **3a** and epicatechin **3b** (Scheme 5). Our preparative results are reported in **table 2**.



3a-3b **5** **4a-4b**

Scheme 5

Table 2. Preparation of 8-Substituted Catechins-5,7,3′,4′-tetramethyl **4** via Suzuki Reaction of Boronic Acid **5** with 8-Iodo-catechin-5,7,3′,4′-tetramethyl Ether **3a** and 8-Iodo-epicatechin-5,7,3′,4′-tetramethyl **3b**.

entry	Boronic acid	3	time (h)	4 yield %
1[a]		3a	5	**4a** 95
2[a]		3b	5	**4b** 95
3[a]		3a	5	**4c** 75
4[a]		3b	5	**4d** 85
5[a]		3a	8	**4e** 90
6[a]		3b	8	**4f** 72
7[a]		3a	24	**4g** 65
8[a]		3b	24	**4h** 60
9[b]		3a	24	**4i** 90
10[b]		3b	24	**4j** 94

[a] Reactions were carried out on a 0.10 mmol scale under argon using 1 equiv. of 3a,3b 1.5 equiv. of boronic acid 0.02 equiv. of $Pd_2(dba)_3$, 0.04 equiv. of S-phos, 0.7 mL of Toluene, and 3 equiv. of K_3PO_4, at 100°C. [b] Reactions were carried out on a 0.10 mmol scale under argon using 1 equiv. of 3a,3b 1.5 equiv. of boronic acid 0.04 equiv. of $Pd_2(dba)_3$, 0.08 equiv. of S-phos, 0.7 mL of Toluene, and 4 equiv. of K_3PO_4, at 120°C. [B] Yields are given for isolated products.

When 8-iodo-catechin-tetramethyl ether **3a** reacted with 4-phenyl boronic acid the starting material has been recovered in almost quantitative yield. Increasing temperature, the amount of palladium and base led to the formation of **4i** and **4j** in excellent yields (Table 2, entries 9 and 10).

Conclusion

In conclusion, we developed an efficient synthesis of new catechin derivatives that can represent a useful approach to the preparation of new polyphenols of which can be tested the biological activities.

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Appendix I. EXPERIMENTAL SECTION

Melting points were determined with a Büchi B-545 apparatus and are uncorrected. All of the reagents, catalysts, and solvents are commercially available and were used as purchased, without further purification. Reaction products were purified on axially compressed columns, packed with SiO_2 25-40 μm (Macherey Nagel), connected to a Gilson solvent delivery system and to a Gilson refractive index detector, and eluting with *n*-hexane/ethyl acetate mixtures. ^{1}H NMR (400 MHz), ^{13}C NMR (100.6 MHz) and ^{19}F NMR (376.5 MHz) spectra were recorded with a Bruker Avance 400 spectrometer. IR spectra were recorded with a Jasco FT/IR-430 spectrometer. Mass spectra were recorded with a Shimadzu GC-MS QP-2010S spectrometer.

Chapter 3-Experimental Section

Typical Procedure for the Preparation of 4-Aryl Coumarins (4) from 3-(*o*-Hydroxyphenyl)acrylate Esters (1) and Aryl Iodides and Bromides (2).

To a stirred solution of **1b** (0.109 g, 0.50 mmol), *p*-bromoanisole (0.093 mL, 0.75 mmol), $^{n}BuN_4OAc$ (0.312 g, 1.05 mmol) and $^{n}BuN_4Br$ (0.239 g, 0.75 mmoli) at 100 °C, $Pd(OAc)_2$ (0.006 g, 0.025 mmol) was added. The mixture was stirred for 8 h at 100 °C. Then, it was diluted with ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (axially compressed column packed with SiO_2, 35 g, 25-40 μm, connected to a Gilson solvent delivery system and to a Gilson refractive index detector) eluting with a 75/25 v/v *n*-hexane/AcOEt mixture) to give 0.110 g (88 % yield) of **4a**: mp: 119-120 °C; IR (KBr): ν = 1729, 1605 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58-7.55 (m, 2H), 7.43-7.39 (m, 3H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.07-7.04 (m, 2H), 6.36 (s, 1H), 3.90 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 160.7, 155.3, 154.1, 142.6, 139.9, 133.9, 131.9, 128.9, 128.9, 127.9, 127.5, 127.1, 126.9, 124.1, 118.9, 117.3, 115.0.

4b: mp:148-149 °C; IR (KBr): 1719, 1597 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.54-7.52 (m, 2H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.03-6.97 (m, 3H), 6.37

(s, 1H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 160.8, 159.9, 155.6, 154.2, 136.5, 132.0, 130.1, 127.1, 124.3, 120.8, 119.0, 117.3, 115.1, 115.1, 114.2, 55.5.

4c: mp: 208-209 °C; IR (KBr): 3192, 1685, 1604, 1200 cm^{-1}; ^{1}H NMR ([d_6]DMSO): δ = 9.95 (bs, 1H), 7.64 (td, J_1 = 1.0 Hz, J_2 = 8.6 Hz , 1H), 7.57 (dd, J_1 = 8.0 Hz, J_2 = 1.3 Hz , 1H), 7.46 (dd, J_1= 1.1 Hz, J_2 = 0.4 Hz , 1H), 7.40 (d, J = 6.6 Hz, 2H), 7.36 (td, J_1= 1.1 Hz, J_2 = 8.1 Hz , 1H), 6.95 (d, J = 6.6 Hz, 2H), 6.34 (s, 1H); ^{13}C NMR ([D_6]DMSO): δ = 160.4, 159.6, 155.6, 154.3, 132.7, 130.8, 127.5, 125.8, 125.0, 119.2, 117.6, 116.3, 114.3.

4d: mp: 151-152°C; IR (KBr): 1715, 1602, 1364 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.71 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 2H), 7.55-7.52 (t, J = 8.0, Hz 1H), 7.42-7.39 (m, 3H), 7.25 (t, J = 8.0 Hz 1H), 6.84-6.81 (m, 2H), 6.35 (s, 1H), 3.07 (s, 6H); ^{13}C NMR ($CDCl_3$): δ = 161.4, 155.9, 154.4, 151.5, 131.6, 129.9, 127.3, 123.9, 122.5, 119.4, 117.4, 113.4, 112.0, 40.3.

4e: mp: 108-109 °C; IR (KBr): 1735, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.56-7.53 (m, 2H), 7.42-7.35 (m, 5H), 7.24 (t, J = 8.0 Hz, 1H), 6.37 (s, 1H), 2.47 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 160.9, 155.8, 154.3, 140.0, 132.4, 131.9, 129.6, 128.5, 127.1, 124.1, 119.2, 117.4, 115.0, 21.4.

4f: mp: 152-153 °C; lit. mp; 141-143 °C. Wattanasin, S. *Synthetic Commun.* **1988**, *18*, 1919.

4g: mp: 108-109 °C; IR (KBr): 1736, 1608 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.57 (t, J = 8.0 Hz, 1H), 7.48-7.43 (m, 4H), 7.27-7.22 (m, 3H), 6.38 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 164.9, 162.4, 160.6, 154.4 (d, J = 38 Hz), 132.1, 131.2 (d, J = 3.5 Hz), 130.4 (d, J = 8.4 Hz), 126.8, 124.3, 118.9, 117.5, 116.1 (d, J = 21.8 Hz), 115.4; ^{19}F NMR ($CDCl_3$): δ{H} = -110.8.

4h: mp: 114-115 °C; IR (KBr): 1718, 1603, 1365, 1180 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.59-7.54 (m, 4H), 7.42-7.40 (m, 3H), 7.24 (t, J = 8.0 Hz, 1H), 6.39 (s, 1H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$): δ = 160.9, 155.7, 154.3, 153.1, 132.3, 131.9, 128.3, 127.2, 125.9, 124.1, 119.1, 117.3, 115.0, 34.9, 31.3.

4i: mp: 209-210 °C; IR (KBr): 3300, 1712, 1666, 1600 cm^{-1}; ^{1}H NMR ([D_6]DMSO): δ = 10.21 (bs, 1H), 7.77 (d, J = 8.6, 2H), 7.65 (td, 1H, J_1 = 1.1 Hz, J_2 = 8.6 Hz , 1H), 7.54 - 7.46 (m, 4H), 7.33 (td, J_1= 1.1 Hz, J_2 = 8.2 Hz , 1H), 6.39 (s, 1H), 2.09 (s, 3H); ^{13}C NMR ([D_6]DMSO): δ = 168.7, 159.7, 154.6, 153.7, 140.8, 132.2, 129.3, 129.0, 126.8, 124.5, 118.9, 118.4, 117.0, 144.2, 24.1.

4j: mp: 185-186 °C; IR (KBr): 1719, 1603 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 10.14 (s, 1H), 8.08-8.04 (m, 2H), 7.66-7.62 (m, 2H), 7.59 (t, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0

Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 2H), 6.42 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 191.4, 160.3, 154.4, 154.3, 141.1, 137.1, 132.4, 130.2, 129.3, 126.6, 124.5, 118.5, 117.6, 115.8.

4k: mp: 137-138 °C; IR (KBr): 1714, 1603, 1253, 1187 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.78-7.76 (m, 2H), 7.70-7.68 (m, 2H), 7.62-7.50 (m, 6H), 7.45-7.42 (m, 2H), 7.28 (t, *J* = 8.0 Hz, 1H), 6.45 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 160.7, 155.3, 154.1, 142.6, 139.9, 133.9, 131.9, 128.9, 128.9, 127.9, 127.5, 127.1, 126.9, 124.1, 118.9, 117.3, 115.0.

4l: mp: 119-120 °C; IR (KBr): 1728, 1607 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.82 (d, *J* = 7.3 Hz, 1H), 7.73-7.68 (m, 3H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.43 (dd, J_1 = 8.3 Hz, J_2 = 1.1 Hz,1H), 7.39 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz,1H), 7.27 (t, *J* = 8.0 Hz, 1H), 6.40 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 160.3, 154.3, 154.1, 136.1, 132.4, 131.8, 131.6 (q, *J* = 32.7 Hz), 129.7, 126.6, 126.5, 125.3 (q, *J* = 3.7 Hz), 124.6, 123.7 (q, *J* = 272.1 Hz), 118.6, 117.6, 115.9; ^{19}F NMR ($CDCl_3$): δ {H} = -63.2.

4m: mp: 195-196 °C; IR (KBr): 1719, 1603 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.68 (d, *J* = 6.6 Hz, 2H), 7.58-7.53 (m, 1H), 7.48-7.40 (m, 2H), 7.38 (d, *J* = 6.6 Hz, 2H), 7.28-7.25 (m, 1H), 6.37 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 160.5, 154.5, 154.2, 134.1, 132.3, 132.2, 130.1, 126.7, 124.4, 124.3, 118.7, 117.5, 115.4.

4n: mp: 172-173 °C; IR (KBr): 1733, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 8.00 (d, *J* = 8.5 Hz, 1H), 7.95-7.90 (m, 3H), 7.65-7.53 (m, 5H), 7.44 (dd, J_1 = 8.3 Hz, J_2 = 0.5 Hz , 1H), 7.24 (td, J_1 = 1.1 Hz, J_2 = 8.2 Hz , 1H), 6.49 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 160.7, 155.7, 154.3, 133.7, 133.1, 132.7, 132.0, 128.7, 128.4, 128.2, 127.9, 127.4, 127.2, 127.1, 125.7, 124.3, 119.2, 117.4, 115.6.

4o: mp: 145-146 °C; IR (KBr): 1728, 1609 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.81-7.78 (m, 2H), 7.69-7.67 (m, 2H), 7.60-7.40 (m, 6H), 7.31-7.27 (m, 2H), 6.50 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 160.4, 158.8 (d, *J* = 244.1 Hz), 154.5 (d, *J* = 2.7 Hz), 150.4, 143.1, 140.0, 133.6, 129.1, 128.9, 128.1, 127.8, 127.3, 120.0 (d, *J* = 8.6 Hz), 119.4 (d, *J* = 24.5 Hz), 118.9 (d, *J* = 8.5 Hz), 116.1, 112.7 (d, *J* = 25.2 Hz); ^{19}F NMR ($CDCl_3$): δ{H} = -117.03.

4p: mp: 154-155 °C; IR (KBr): 1731, 1564, 1426, 1253, 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 8.02 (d, *J* = 8.5 Hz, 1H), 7.98-7.92 (m, 3H), 7.66-7.58 (m, 2H), 7.53 (dd, J_1 = 8.5 Hz, J_2 = 1.7 Hz, 2H), 7.42-7.40 (m, 2H), 7.33-7.20 (m, 2H), 6.54 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 160.5, 158.8 (d, *J* = 244.1 Hz), 155.0 (d, *J* = 2.7 Hz), 150.5 (d, *J* = 1.9 Hz), 133.8, 133.2, 132.2, 129.1, 128.6,

128.2, 128.1, 127.7, 127.3, 125.5, 120.2 (d, *J* = 8.6 Hz), 119.5 (d, *J* = 24.5 Hz), 119.0 (d, *J* = 8.4 Hz), 116.5, 112.8 (d, *J* = 25.2 Hz); ^{19}F NMR ($CDCl_3$): δ {H} = -116.74.

4q: mp: 159-160 °C; IR (KBr): 1732, 1609, 1253, 1178 $cm^{-1}cm^{-1}$; ^{1}H NMR ($CDCl_3$): δ = 7.44-7.36 (m, 3H), 7.30-7.24 (m, 2H), 7.09-7.04 (m, 2H), 6.41 (s, 1H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 161.1, 160.6, 158.7 (d, *J* = 243.3 Hz), 154.5 (d, *J* = 2.7 Hz), 150.4 (d, *J* = 1.9 Hz), 129.9, 127.0, 120.2 (d, *J* = 8.5 Hz), 119.2 (d, *J* = 24.5 Hz), 118.9 (d, *J* = 8.4 Hz), 115.6, 114.6, 112.7 (d, *J* = 25.2 Hz), 55.6; ^{19}F NMR ($CDCl_3$): δ{H} = -117.07.

4r: mp: 161-162 °C; IR (KBr): 1722, 1610, 1251, 1183 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.84-7.81 (m, 2H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 1H), 7.06-7.03 (m, 2H), 6.64 (s, 1H), 3.91 (s, 3H), 2.62 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 161.4, 160.4, 154.9, 154.3, 149.4, 135.8, 131.7, 126.2, 125.7, 125.0, 116.3, 113.8, 55.4, 24.3.

4s: mp: 158-159 °C; IR (KBr): 1724, 1604, 1250, 1182 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.55-7.49 (m, 2H), 7.43-7.40 (m, 2H), 7.36 (d, *J* = 8.7 Hz, 1H), 7.10-7.07 (m, 2H), 6.39 (s, 1H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 161.2, 160.4, 154.4, 152.8, 131.9, 130.0, 129.7, 126.9, 126.5, 120.5, 118.9, 115.6, 114.7, 55.6.

Chapter 4-Experimental Section

Typical procedure for the reaction of β-arylacrylamides with *p*-iodoanisole: to a stirred solution of **1h** (0.113 g, 0.50 mmol), *p*-iodoanisole (0.093 mg, 0.75 mmol) and Et_3N (348 µl, 2.5 mmol), $Pd(OAc)_2$ (0.006 g, 0.025 mmol) was added. The reaction mixture was stirred for 12 h at 100 °C. Then, the mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 35 g; *n*-hexane/ethyl acetate 30/70 v/v) to give 0.144 g (87 % yield) of 2h: m.p. = 163-165°C; IR (KBr) 3294, 3177, 1654 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.69 (dd, J = 8.4 and 1.33 Hz, 1 H), 7.43 (m, 1 H), 7.32-7.27 (m, 3 H), 7.23-7.21 (m, 2 H), 6.87-6.85 (m, 2 H), 6.49 (s, 1 H) 5.28-5.16 (d, 2 H),1.61(s, 3H); ^{13}C NMR ($CDCl_3$) δ 167.2, 160.1, 148.6, 139.0, 132.8, 130.3, 130.2, 129.4, 128.1, 127.4, 122.3, 119.7, 113.6, 54.8; MS: m/z (relative intensity) 332 (M^+100%), 334 (73%),252 (54%). Anal Calcd for $C_{16}H_{14}BrNO_2$: C, 57.85; H, 4.25; Br, 24.05; N; 4.22. Found: C, 57.77; H, 4.28; Br, 24.02; N, 4.26.

Appendix I. EXPERIMENTAL SECTION

Typical procedure for the reaction of β-arylacrylamides with ethyl *p*-iodobenzoate: to a stirred solution of **1h** (0.113 g, 0.50 mmol), ethyl *p*-iodobenzoate (209 µl, 1.25 mmol) and Et_3N (348 µl, 2.5 mmol), $Pd(OAc)_2$ (0.001 g, 0.005 mmol) was added. The reaction mixture was stirred for 24 h at 100 °C. Then, the mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 35 g; *n*-hexane/ethyl acetate 25/75 v/v) to give 0.152 g (82 % yield) of **2ac**: m.p.: 235-237 °C; IR (KBr) 3338, 3181, 1668 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.03 (d, *J* = 8.3 Hz, 2 H), 7.69 (d, *J* = 8.4 Hz, 1 H), 7.45 (t, J = 7.6 Hz, 1 H), 7.35-7.30 (m, 4 H), 6.61 (s, 1 H) 5.32-5.25 (d, 2 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 1.38 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.5, 165.5, 147.9, 142.1, 138.2, 132.9, 130.4, 130.3, 129.8, 129.3, 127.5, 126.6, 123.5, 122.2, 60.6, 13.8; MS: m/z (relative intensity) 374 (M^+50 %), 376 (100 %), 294 (34%). Anal Calcd for $C_{18}H_{16}BrNO_3$: C, 57.77; H, 4.31; Br, 21.35; N; 3.74. Found: C, 57.69; H, 4.35; Br, 21.38; N, 3.70.

Typical procedure for the preparation of 2-quinolones (4): to a stirred solution of **1h** (0.113 g, 0.50 mmol), *p*-iodoanisole (0.093 g, 0.75 mmol) and Et_3N (348µl, 2.5 mmol), $Pd(OAc)_2$ (0.006 g, 0.025 mmol) was added. The reaction mixture was stirred for 12 h at 100 °C. then, the mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. 2mL of dioxane, CuI (0.019 g, 0.1 mmol), NaI (0.149 g, 1 mmol), K_3PO_4 (0.212 g, 1 mmol), *N,N*-dimethylethylendiammine (21.3 µl, 0.2 mmol) and were added to the crude mixture. The mixture was stirred for 24 h at 120°C. Then, the mixture was diluted with ethyl acetate and washed with a saturated NH_4Cl solution. The organic layer was dried over Na_2SO_4 concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 35 g; *n*-hexane/ethyl acetate 30/70 v/v) to give 0.97 g (77 % yield) of **4b**: m.p. = 196-198 °C; IR (KBr) 3131, 1672 cm^{-1}; ^1H NMR ($DMSO_{d6}$) δ 11.82 (s, 1 H), 7.51 (t, *J* = 8 Hz, 1 H), 7.44-7.36 (m, 4 H), 7.13-7.07 (m, 3 H), 6.34 (s, 1H), 3.82 (s, 3 H); ^{13}C NMR ($DMSO_{d6}$) δ 161.3, 159.6, 151.1, 139.3, 130.4, 130.1, 128.8, 126.2, 121.7, 120.9, 118.5, 115.8, 114.1, 55.2; MS: m/z (relative intensity) 251 (M^+100 %), 252 (25 %), 236 (25%) 220 (12%). Anal Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N; 5.57. Found: C, 76.55; H, 5.18; N, 5.53.

Chapter 5-Experimental Section

Synthesis of (1) - To a stirred solution of acrylamide (74.5 mg, 1.05 mmol), 1-bromo-2-iodobenzene (128 µL, 1mmol) and NEt_3 µL, 3 mmol) in CH_3CN (1 mL), Hermann catalyst (9.36 mg, 0.01 mmol) was added. The reaction mixture was stirred for 12 h at 100°C. After cooling, the reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 35 g; 40/60 v/v *n*-hexane/ethyl acetate) to give 180 mg of 1: m.p.:171-173 °C; IR (KBr) 3340, 3153, 1671 cm^{-1}; ^1H NMR ($DMSO_{d6}$) δ 7.70-7.63 (m, 4H), 7.44 (m, 1H), 7.32 (m, 1H), 7.24 (bs, 1H), 6.63 (d, J = 15.64 Hz, 1H); ^{13}C NMR ($DMSO_{d6}$) δ 166.6, 137.7, 135.0, 133.7, 131.6, 128.8, 128.2, 126.0, 124.7; MS: *m/z* (relative intensity) 226.90 (4.25%), 225.95(0.78 %), 224.90 (M^+, 4.29 %),146.10 (100.00%), 102.10 (34.45 %), 44 (41.00%).

Typical Procedure for the Preparation of 4-Aryl-2-quinolones (4) - To a mixture of 1 (0.113 g, 0.50 mmol), *p*-iodoanisole (0.093 mL, 0.75 mmol), *n*-Bu_4OAc (0.452 g, 1.5 mmol) and *n*-Bu_4Br (0.483 g, 1.5 mmol), $Pd(OAc)_2$ (0.006 g, 0.025 mmol) was added. The mixture was stirred for 48 h at 120 °C. After cooling, the reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 35 g; 25/75 v/v *n*-hexane/ethyl acetate) to give 0.092 g (73 % yield) of **4a**: m.p.: 196-198 °C; IR (KBr) 3131, 1672 cm^{-1}; ^1H NMR ($DMSO_{d6}$) δ 11.82 (bs, 1H), 7.51 (t, J = 8 Hz, 1H), 7.44-7.36 (m, 4H), 7.13-7.07 (m, 3H), 6.35 (s, 1H), 3.82 (s, 3H); ^{13}C NMR ($DMSO_{d6}$) δ 161.3, 159.6, 151.1, 139.3, 130.4, 130.1, 128.8, 126.2, 121.7, 120.9, 118.5, 115.8, 114.1, 55.2; MS *m/z* (relative intensity) 251 (M^+, 100 %), 252 (40 %), 236 (30%) 208 (50 %).

4b: m.p: 229-231 °C; IR (KBr) 3140, 1667 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.53 (bs, 1H), 7.61-7.59 (m, 3H), 7.54-7.27 (m, 4H), 7.18 (t, J = 8 Hz, 1H), 6.70 (s, 1H), 2.47 (s, 3H);^{13}C NMR ($DMSO_{d6}$) δ 161.9, 152.0, 139.9, 138.8, 134.4, 131.0, 129.8, 129.1, 126.7, 122.3, 121.6, 118.9, 116.3, 21.4; MS *m/z* (relative intensity) 235 (M^+, 100 %), 236 (17%), 220 (20 %) 220 (50 %).

4c: m.p.: 189-192 °C; IR (KBr); 3138, 1661 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.58 (bs, 1H), 7.62-7.60 (m, 1H), 7.56 (m, 2H), 7.45-7.43 (m, 1H), 7.19 (m, 1H), 7.09-7.03 (m, 3H), 6.74 (s, 1H), 3.88 (s, 3H); ^{13}C NMR ($DMSO_{d6}$) δ 161.3, 159.3, 151.3, 139.2, 138.0, 130.5, 129.8, 126.2, 121.9, 121.1, 120.8, 118.3, 115.7, 114.4, 114.1, 55.2; MS *m/z* (relative intensity) 251 (M^+, 100 %), 252 (25 %), 236 (15%) 220 (45 %).

4d: m.p.: 235-237°C; IR (KBr) 3063, 1670 cm^{-1}; ^{1}H NMR ($DMSO_{d6}$) δ 11.92 (bs, 1H), 7.58-7.54 (m, 2H), 7.42-7.18 (m, 5H), 7.17-7.16 (m, 1H), 6.44 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 163.7, 162.7 (d, *J* = 247 Hz), 151.9, 139.3 (d, *J* = 7.8 Hz), 139.0, 130.9, 130.4 (d, *J* = 8.3 Hz), 126.6, 124.7(d, *J* = 2.9 Hz), 122.7, 121.2, 119.3, 116.7, 116.4 (d, *J* = 20.7 Hz), 115.8 (d, *J* = 19.4 Hz); ^{19}F NMR δ -112.4; MS *m/z* (relative intensity) 239 (M^+, 100 %), 241 (16 %), 211 (85 %), 183(65%).

4e: m.p.: 202-204 °C; IR(KBr) 3134, 1665cm^{-1}; ^{1}H NMR ($DMSO_{d6}$) δ 11.92 (bs, 1H), 7.90-7.78 (m, 4H), 7.55-7.16 (m, 4H), 6.48 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 163.8, 152.0, 139.0, 138.0, 131.3, 131.4(q, *J* = 32.4 Hz,), 131.2, 129.4, 126.3, 125.7 (m, 2C), 123.9 (q, *J* = 272.0 Hz),123.0, 121.5, 119.3, 116.9 ; ^{19}F NMR δ-61.0; MS *m/z* (relative intensity) 289 (M^+, 100 %), 290 (16 %), 261 (40 %), 220 (25%), 165 (35 %), 69 (45%).

4f: m.p.: 224-225 °C; IR (KBr) 3133, 1669 cm^{-1}; ^{1}H NMR ($DMSO_{d6}$) δ 11.94 (bs, 1H), 8.12-8.10 (m, 2H), 7.65-7.62 (m, 2H), 7.55-7.53 (m, 1H), 7.42-7.40 (m, 1H), 7.34-7.32 (m, 1H), 7.17-7.13, (m, 1H) 6.45 (s, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($DMSO_{d6}$) δ 165.9, 161.6, 150.9, 141.8, 139.8, 131.3, 130.6, 129.9, 129.7, 126.5, 122.5, 122.0, 118.5, 116.4, 61.4, 14.7; MS *m/z* (relative intensity) 293 (M^+, 100 %), 294 (19 %), 237 (37%), 56 (20%).

4g: m.p.: 201-203 °C; IR (KBr) 3066, 1668 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.96 (bs, 1H), 7.60-7.49 (m, 3H), 7.50-7.36 (m, 3H), 7.14-7.13, (m, 2H), 6.47 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 163.9, 159.5(d, *J* = 248 Hz), 148.0, 138.6, 131.1 (d, *J* = 3.1 Hz), 131.0, 130.9, 126.6, 124.7(d, *J* = 15.9 Hz), 124.6 (d, *J* = 3.6 Hz), 122.8, 122.3, 119.6, 116.6, 116.1 (d, *J* = 21.4 Hz); ^{19}F NMR (δ) -111.7; MS *m/z* (relative intensity) 239 (M^+, 100 %), 240 (12 %), 211 (60%), 183 (75%).

4i: m.p.: 191-193 °C; IR (KBr) 3138, 1669cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.69 (bs, 1H), 7.65-7.64 (m, 2H), 7.63-7.50 (m, 5H), 7.20-7.18 (m, 1H), 6.74 (s, 1H), 5.92 (s, 1H), 4.20-4.07(m, 4H); ^{13}C NMR ($CDCl_3$) δ 164.2, 153.3, 139.0, 138.7, 137.3, 130.9, 129.8, 128.8, 127.2, 127.1, 126.8,

122.8, 121.0, 119.7, 116.8, 103.5, 65.5; MS *m/z* (relative intensity) 292 (M^+, 100 %), 293 (100 %), 294 (19,8%).

4k: m.p.: 119-120 °C; IR (KBr) 3133, 1667cm^{-1};^{1}H NMR ($DMSO_{d6}$) δ 11.87 (bs, 1H), 7.59-7.37 (m, 7H), 7.14 (t, *J* = 7.22, 1H), 6.40 (s, 1H), 4.02-3.75 (m, 4H) 1.62 (s, 3H); ^{13}C NMR ($DMSO_{d6}$) δ 161.2, 151.1, 143.8, 139.3, 136.1, 130.5, 128.6, 126.1, 125.4, 121.9, 121.2, 118.2, 115.8, 107.9, 64.2, 27.2; MS *m/z* (relative intensity): 307 (M^+, 100%), 308 (21%).

4l: m.p.: 276-278 °C; IR (KBr) 3037,1732, 1660 cm^{-1};^{1}H NMR ($CDCl_3$) δ 12.08 (bs, 1H), 7.60-7.48 (m, 5H), 7.39-7.33 (m, 2H), 7.24-7.20 (m, 1H), 6.72 (s, 1H), 3.32(s, 3H), 2.06(s, 3H); ^{13}C NMR ($DMSO_{d6}$) δ 169.7, 161.8, 151.2, 145.2, 139.9, 136.1, 131.2, 130.4, 129.7, 128.4, 127.8, 126.6, 122.5, 121.9, 118.8, 116.4, 37.2, 22.9; MS *m/z* (relative intensity) 292 (M^+, 100 %), 293 (12 %).

4m: m.p.: 263-265 °C; IR (KBr) 3130,1735, 1660 cm^{-1};^{1}H NMR ($CDCl_3$) δ 12.07 (bs, 1H), 7.70-7.34 (m, 7H), 7.22-7.20 (m, 1H), 6.70 (s, 1H), 3.24 (s, 3H), 2.06 (s, 3H); ^{13}C NMR ($DMSO_{d6}$) δ 167.4, 161.8, 151.0, 145.2, 139.9, 136.3, 131.2, 130.4, 129.5, 128.2, 127.8, 126.6, 122.5, 122.0, 118.7, 116.4, 37.2, 22.9; MS *m/z* (relative intensity) 292 (M^+, 100 %), 293 (25 %).

4n: m.p: 252-254 °C; IR (KBr) 3170, 1624 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.69 (bs, 1H), 7.59-7.48 (m, 8H), 7.21-7.17 (m, 1H), 6.73 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 164.1, 153.5, 139.0, 137.2, 130.7, 129.0, 128.9, 128.7, 128.5, 127.3, 126.8, 122.6, 120.9, 119.7, 116.7;MS *m/z* (relative intensity) 221 (M^+, 100 %), 222 (27%), 220 (36 %), 207 (38 %).

Chapter 6-Experimental Section

Typical Procedure for preparation of Benzo[*b*]furans (3) from *o*-Iodocardanol (1) and terminal alkynes (2): To a stirred solution of **1** (100 mg, 0.23 mmol) and $PdCl_2(PPh_3)_2$ (3.2 mg, 0.02 mmol), in Et_2NH (0.3 mL) and dry DMF (0.2 mL) under Ar at 60°C, CuI (2 mg, 0.04 mmol) and *m*-methoxyphenylacetylene (37 mg, 0.28 mmol) were added. After 0.5 h the temperature was increased to 80°C and the reaction mixture was maintained at that temperature for 5 h. After this time, the mixture was diluted with ethyl acetate and washed with brine. The organic extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 35 g; n-hexane) to give 70

mg of **3e** (70% yield): mp 48-49°C;IR (KBr): 2913, 2850 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.49-7.34 (m, 5 H), 7.09-7.07 (d, *J* = 7.78 Hz, 1 H), 7.00 (s, 1 H), 6.92-6.89 (d, *J* = 9.9 Hz, 1 H), 3.90 (s, 3 H), 2.75-2.72 (t, *J* = 7.6 Hz, 2 H), 1.70-1. 65 (m, 2 H) 1.34-1.27 (m, 24 H), 0.92-0.88 (t, *J* = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$): δ 160.0, 155.4, 155.3, 140.0, 132.1, 129.9, 127.0, 124.0, 120.5, 117.4, 114.3, 110.8, 110.0, 101.6, 55.4, 36.3, 32.0, 31.9, 29.8, 29.7, 29.6, 29.4, 29.3, 22.8, 14.2.

MS (EI, 70 ev): *m/z* (%) = 434 (M+, 100), 237 (86), 43 (48.49), 435 (33), 41 (28); Anal. Calcd for $C_{30}H_{42}O_2$: C, 82.90; H, 9.74. Found C, 82.88; H, 9.76.

3a: mp 49-50°C;IR (KBr): 3340, 2916, 2849 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.44-7.41 (d, *J* = 8.2 Hz, 1 H), 6.8 (s, 1 H), 6.74-6.72 (d, *J* = 8.2 Hz, 1 H), 2.60-2.58 (s, 6 H), 1.66-1.61 (m, 2 H), 1.31-1.26 (m, 26 H), 0.91-0.88 (t, *J* = 6.5, 3 H); ^{13}C NMR ($CDCl_3$): δ 162.4, 155. 1, 139.6, 126.0, 123.6, 120.5, 110.8, 100.2, 69.3, 36.2, 32.0, 29.7 29.6 29.5, 29.4, 29.3, 28.8, 22.7, 14.2; MS (EI, 70 ev): *m/z* (%) = 43 (100), 171 (73), 371 (72), 368 (57), 41 (49), 57 (20), 386 (M^+, 18); Anal. Calcd for $C_{26}H_{42}O_2$: C, 80.77; H, 10.95. Found C, 80.70; H, 10.92.

3b: mp 47-48 °C; IR (KBr): 2918, 2849 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.41-7.23 (m, 7 H), 7.07-7.01 (dd, *J* = 7.9, *J* = 1.3 Hz, 1 H), 6.33 (s, 1 H), 3.10-3.08 (m, 4 H), 2.76-2.72 (t, *J* = 7.6, 2 H), 1.71-1. 66 (m, 2 H) 1.35-1.23 (m, 24 H), 0.95-0.92 (t, *J* = 6.5, 3 H); ^{13}C NMR ($CDCl_3$): δ 157.9, 155.1, 130.8, 128,5, 128.4, 126.6, 126.2, 123.3,`119.8, 141.1, 138.8, 113.9, 110.5, 102.2, 55.4, 36.2, 34.1, 32.1, 30.5, 29.8, 29.7, 29.7, 29.5, 29.4, 22.8, 14.2; MS (EI, 70 ev): *m/z* (%) = 145 (100), 43 (53),432 (M^+, 51), 91.05 (32) 41 (29), 433 (17); Anal. Calcd for $C_{31}H_{44}O$: C, 86.05; H, 10.25. Found: C, 86.10; H, 10.29.

3c:Oil;IR (KBr): 2925, 2853 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.40-7.38 (d, *J* = 7.9 Hz, 1 H), 7.26 (s, 1 H), 7.05-7.03 (dd, *J* = 7.9, J = 1.3 Hz, 1 H), 6.34 (s, 1H), 2.74-2.71 (t, *J* = 7.6, 2 H), 2.66-2.64 (d, *J* = 6.5 Hz, 2 H), 1.81-1.75 (m, 10 H), 1.35-1.04 (m, 26 H), 0.94-0.91 (t, *J* = 6.5, 3 H); ^{13}C NMR ($CDCl_3$): δ 157.9, 155.1, 138.5, 126.7, 123.2, 119.6, 110.4, 102.7, 37.1, 36.4, 36.2, 33.3, 32.1, 32.0, 29.8, 29.7, 29.6, 29.5, 29.4, 26.5, 26.3, 22.8, 14.2; MS (EI, 70 ev): *m/z* (%) = 424 (M^+,100), 43 (64), 145 (52), 55 (38), 41 (42), 425 (34); Anal. Calcd for $C_{30}H_{42}O$: C, 84.84; H, 11.39. Found C, 84.77; H, 11.30.

3d:mp 57-58 °C; IR (KBr): 2917, 2849 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.11-8.09 (dd, *J* = 7.8, *J* = 1.7 Hz, 1 H), 7.53-7.51 (d, *J* = 7.8 Hz, 1 H), 7.40-7.32 (m, 3 H), 7.14-7.08 (m, 2 H), 7.04-7.03 (d, *J* = 7.8 Hz, 1 H), 4.03 (s, 3 H), 2.79-2.75 (t, *J* = 7.6, 2 H), 1.74-1. 68 (m, 2 H) 1.37-1.30 (m, 24 H), 0.94-0.91 (t, *J* = 6.5, 3 H); ^{13}C NMR ($CDCl_3$): δ 156.4, 154.4, 151.7, 139.8, 129.0, 127.6, 126.9 123.6, 120.8, 120.6, 119.7, 111.1, 110.5, 106.4, 55.5, 36.7, 32.0, 32.0, 29.8, 29.7, 29.6 29.5, 29.4 22.8,14.2; MS (EI, 70 ev): *m/z* (%) = 434 (M^+,100), 237 (68), 43 (50), 435 (35), 41 (32), 207 (22); Anal. Calcd for $C_{30}H_{42}O_2$: C, 82.90; H, 9.74. Found C, 82.84; H, 9.79.

3f: mp 83-84 °C; IR (KBr): 3334, 2917, 2848 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.87 (s, 1 H), 7.79-7.77 (d, *J* = 7.4 Hz, 1 H), 7.49-7.42 (m, 2 H), 7.34 (bs, 2 H), 7.09-7.07 (d, *J* = 8 Hz, 1 H), 7.01 (s, 1 H), 4.79 (s, 2 H), 2.76-2.72 (t, *J* = 7.6, 2 H), 1.69-1. 64 (m, 2 H), 1.34-1.27 (m, 24 H), 0.91-0.87 (t, *J* = 6.5, 3 H); ^{13}C NMR ($CDCl_3$): δ 155.4, 155.2, 141.5, 140.1, 131.1, 129.1, 126.8, 124.1, 123.9, 123.2, 120.5, 110.8, 101.5, 65.3, 36.3, 32.0, 31.9, 29.8, 29.7, 29.6, 29.4, 29.3, 22.8, 14.2; MS (EI, 70 ev): *m/z* (%) = 43 (100), 434 (M^+, 96), 417 (56), 41 (56), 418 (34), 57 (35); Anal. Calcd for $C_{30}H_{42}O_2$: C, 82.90; H, 9.74. Found C, 82.86; H, 9.77.

3g: mp 174-175°C; IR (KBr): 3278, 2918, 2849 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 10.11 (bs, 1 H), 7.81-7.79 (d, *J* = 8.5 Hz, 2 H), 7.61-7.59 (d, *J* = 8.5 Hz, 2 H), 7.49-7.47 (d, *J* = 7.6 Hz, 1 H), 7.31 (s, 1 H), 7.08-7.06 (d, *J* = 7.6 Hz, 1 H), 6.92 (s, 1 H), 2.75-2.71 (t, *J* = 7.6, 2 H), 2.23 (s, 3 H), 1.70-1. 65 (m, 2 H) 1.34-1.27 (m, 24 H), 0.91-0.87 (t, *J* = 6.5, 3 H); ^{13}C NMR ($CDCl_3$): δ 169.1, 156.2, 155.4, 136.4, 131.9, 127.4, 123.2, 121.5, 114.5, 110.3, 101.9, 36.3, 32.0, 31.9, 29.8, 29.7, 29.6, 29.5, 29.4, 22.8, 21.8 14.2; MS (EI, 70 ev): *m/z* (%) = 461.40 (M^+,100.00%), 43.00 (75.58%), 264.10 (41.97 %),462.40 (34.03%), 222.05 (24.51 %),41.05 (20.52%); Anal. Calcd for $C_{31}H_{43}NO_2$: C, 80.65; H, 9.39; N, 3.03. Found C, 80.70; H, 9.36; N, 3.05.

3h: mp 72-73°C; IR (KBr): 3452, 2915, 2847, 1521 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.43 (s, 1 H), 7.95-7.92 (m,1 H), 7.51-7.49 (m, 1 H), 7.42-7.40 (m, 1 H), 7.36 (s, 1 H), 7.12-7.07 (m, 2 H), 2.76-2.73 (t, *J* = 7.6 Hz, 2 H), 2.65 (s, 3 H), 1.70-1. 65 (m, 2 H) 1.34-1.27 (m, 24 H), 0.91-0.87 (t, *J* = 6.5 Hz, 3 H);^{13}C NMR ($CDCl_3$): δ 160.0, 155.4, 155.3, 140.0, 132.1, 129.9, 127.0, 124.0, 120.5, 117.4, 114.3, 110.8, 110.0, 101.6, 55.4, 36.3, 32.0, 31.9, 29.8, 29.7, 29.6, 29.4, 29.3, 22.8, 14.2; MS (EI, 70 ev): *m/z* (%) = 463 (M^+, 100), 43 (70), 266 (69),41.00 (40), 464 (35); Anal. Calcd for $C_{30}H_{41}NO_3$: C, 77.71; H, 8.91; N, 3.02. Found 77.68; H, 8.93; N, 3.05.

3i: mp 108 -109 °C; IR (KBr): 2918, 2849, 1723 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.13-8.11 (d, *J* = 8.4 Hz, 2 H), 7.93-7.91 (d, *J* = 8.4 Hz, 2 H), 7.55-7.52 (d, *J* = 7.9 Hz, 1 H), 7.37 (s, 1 H), 7.13-7.09 (m, 2 H), 3.96 (s, 3 H), 2.77-2.74 (t, *J* = 7.6, 2 H), 1.72-1. 65 (m, 2 H) 1.34-1.26 (m, 24 H), 0.92-0.88 (t, *J* = 6.5, 3 H); ^{13}C NMR ($CDCl_3$): δ 166.8, 155.7, 154.2, 140.9, 110.9, 103.5, 52.2, 36.3, 35.5, 32.0, 31.9, 29.8, 29.8, 29.7, 29.7, 29.5, 29.4, 29.4, 22.8, 14.2; MS (EI, 70 ev): *m/z* (%) = 265 (100), 462 (M^+, 91), 43 (49), 207 (36), 463 (33), 41 (29); Anal. Calcd for $C_{31}H_{42}O_3$: C, 80.48; H, 9.15. Found C, 80.53; H, 9.12.

3j: mp 84-85 °C: IR (KBr): 2917, 2848 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.80-7.78 (d, *J* = 8.2 Hz, 2 H), 7.51-7.49 (d, *J* = 8.7. Hz, 1 H), 7.35 (s, 1 H), 7.10-7.08 (d, *J* = 7.6 Hz, 1 H), 6.99 (s, 1 H), 2.77-2.73 (t, *J* = 7.6, 2 H), 1.71-1. 67 (m, 2 H) 1.35-1.28 (m, 24 H), 0.92-0.88 (t, *J* = 6.5, 3 H); ^{13}C NMR ($CDCl_3$): δ 155.4, 154.3, 140.3, 134.0, 133.8, 129.3, 129.1, 129.0,126.8, 126.0, 124.1, 120.5, 110.8,101.7, 36.3, 32.0, 31.9, 29.8, 29.7, 29.6, 29.4, 29.3, 22.8, 14.2; MS (EI, 70 ev): *m/z* (%) = 438 (M^+, 100), 241 (98), 43 (43), 440 (37), 243 (33), 41 (26); Anal. Calcd for $C_{29}H_{39}ClO$: C, 79.33; H, 8.95; Cl, 8.07. Found C, 79.40; H, 8.90; Cl, 8.03.

3k: mp 98-99 °C; IR (KBr): 2916, 2848, 1676 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.03-8.01 (d, *J* = 8.5 Hz, 2 H), 7.61-7.59 (d, *J* = 8.5 Hz, 2 H), 7.49-7.47 (d, *J* = 8.0 Hz, 1 H), 7.35 (s, 1 H), 7.11-7.08 (m, 2 H), 2.76-2.72 (t, *J* = 7.6, 2 H), 2.62 (s, 3 H), 1.68-1. 66 (m, 2 H) 1.34-1.26 (m, 24 H), 0.91-0.87 (t, *J* = 6.5, 3 H); ^{13}C NMR ($CDCl_3$): δ 197.5, 155.8, 154.1,141. 0, 136.4, 135.0, 129.0, 126.7, 124.6, 124. 3, 120.7, 111.0, 103.7, 36.3, 32.0, 31.9, 29.8, 29.7, 29.6, 29.5, 29.4 29.3,26.7, 22.8, 14.2; MS (EI, 70 ev): *m/z* (%) = 249 (100), 446 (M^+, 69), 447 (30), 43 (24), 448 (4); Anal. Calcd for $C_{31}H_{42}O_2$: C, 83.36; H, 9.48. Found C, 83.40; H, 9.45.

3l: mp 66-67 °C: IR (KBr): 2915, 2848 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.87-7.85 (m, 2 H), 7.51-7.45 (m, 3 H), 7.38-7.34 (m, 2 H), 7.11-7.10 (m, 1 H), 7.01 (s, 1 H), 2.76-2.72 (t, *J* = 7.58, 2 H), 1.72-1. 67 (m, 2 H) 1.37-1.30 (m, 24 H), 0.94-0.90 (t, *J* = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$): δ 155.5, 155.4, 139.9, 130.8, 128.8, 128.3, 127.0, 124.8, 123.9, 120.4, 110.8, 36.3, 32.0, 31.9, 29.8, 29.7, 29.6, 29.5, 29.4, 22.8, 14.2; MS (EI, 70 ev): *m/z* (%) = 207 (100), 404 (M^+, 91), 43 (43), 405 (29), 41.05 (25), 42 (5) 406 (5); Anal. Calcd for $C_{29}H_{40}O$: C, 86.08; H, 9.96. Found C, 86.11; H, 9.93.

3m: mp 72-73 °C; IR (KBr): 3287, 2920, 2849, 1656 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.40-7.38 (d, *J* = 8.0 Hz, 1 H), 7.21 (s, 1 H), 7.02-7.00 (d, *J* = 8.0 Hz, 1 H), 6.57(s, 1 H), 5.53 (bs, 1 H), 2.70-

2.67 (m, 2 H), 2.42-2.39 (m, 2 H), 1.66-1.61 (m, 2 H), 2.06-1.99 (m, 2 H), 1.98 (s, 3 H), 1.65-1.26 (m, 32 H), 0.91-0.88 (t, *J* = 6.5, 3 H); ^{13}C NMR ($CDCl_3$): δ 169.3, 159.8, 154.8, 139.2, 126.2, 125.8, 123.4, 120.5, 110.6, 102.5, 55.5, 36.2, 34.2, 32.0, 31.9, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 25.5, 24.4, 22.7, 21.9, 14.2; MS (EI, 70 ev): *m/z* (%) = 43.05 (100%), 171.10 (73.43 %), 371.30 (72.07 %), 368.40 (56.90 %), 41.05 (48.63 %), 57.10 (20.48%), 386.40 (M^+,18.12 %); Anal. Calcd for $C_{31}H_{49}NO_2$: C, 79.60; H, 10.56; N, 2.99. Found C, 79.51; H, 10.59; N, 2.90.

3n: mp 46-47 °C; IR (KBr): 3515.6, 3420.14, 2919.70, 2848.35 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.53-7.51 (d, *J* = 7.8 Hz, 1 H), 7.39-7.36 (m, 2 H), 7.14-7.12 (dd, *J* = 7.9, *J* = 1.3 Hz, 1 H), 6.97 (s, 1 H), 6.93-6.92 (m, 1 H), 4.27 (bs, 2 H), 2.80-2.77 (t, *J* = 7.6, 2 H), 2.34 (s, 3 H), 2.26 (s, 3 H), 1.74-1. 68 (m, 2 H) 1.37-1.30 (m, 24 H), 0.94-0.91 (t, *J* = 6.5, 3 H); ^{13}C NMR ($CDCl_3$): δ 155.6, 154.8, 140.1, 139.6, 131.9, 127.2, 126.8, 126.8, 123.8, 123.5, 120.2, 115.6 110.7, 103.1, 36.3, 32.5, 32,0, 29.8, 29.8, 29.7, 29.7, 29.5, 29.4, 22.8, 20.5, 17.9, 14.2; MS (EI, 70 ev): *m/z* (%) = 447 (M^+), 250.15(45), 43 (41), 448 (37), 207 (23), 449 (7); Anal. Calcd for $C_{31}H_{45}NO$: C, 83.17; H, 10.13; N, 3.13. Found C, 83.23; H, 10.10; N, 3.15.

Typical Procedure for preparation of Benzo[*b*]furans (3) from *o*-Ethynylcardanol (9) and Aryl Iodides (10): To a stirred solution of *p*-iodoanisole (112 mg, 0.48 mmol), $PdCl_2[PPh_3]_2$ (4.5 mg, 0.006 mmol) in Et_2NH (0.3 mL) and dry DMF (0.2 mL) under Ar at 60°C, CuI (2.4 mg, 0.012 mmol) and **9** (100 mg, 0.32 mmol) were added. After 8h the mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 35 g; *n*-hexane) to give 90 mg of **3o** (70%): mp 108-109°C; IR (KBr) 2917, 2850 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.81-7.79 (d, *J* = 8.7 Hz, 2 H), 7.47-7.45 (d, *J* = 7.9 Hz, 1 H), 7.34 (s, 1 H), 7.08-7.06 (d, *J* = 7 Hz, 1 H), 7.01-6.98 (d, *J* = 7 Hz, 1 H),6.86 (s, 1 H), 3.89 (s, 3 H), 2.76-2.72 (t, *J* = 7.6, 2 H), 1.72-1. 65 (m, 2 H), 1.34-1.26 (m, 24 H), 0.92-0.88 (t, *J* = 6.5, 3 H); ^{13}C NMR ($CDCl_3$): δ 159.9, 155.6, 155.2, 135.2, 128.7, 127.2,126.3, 123.8, 120.2, 114.3,110.7, 99.7, 55.5, 36.3, 32.0, 31.9, 29.8, 29.7, 29.6, 29.5, 29.4, 29.4, 22.8, 14.2; MS (EI, 70 ev): *m/z* (%) = 434 (M^+), 237 (67), 43 (35), 435 (35), 41.00 (19); Anal. Calcd for $C_{30}H_{42}O_2$: C, 82.90; H, 9.74. Found C, 82.85; H, 9.79.

3p: mp 71-72 °C; IR (KBr): 2917, 2848 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.65-7.63 (d, *J* = 7.8 Hz, 1 H), 7.51-7.36 (m, 4 H), 7.12-7.03 (m, 2 H), 7.02 (s, 1 H), 2.77-2.74 (t, *J* = 7.6 Hz, 2 H), 1.72-1. 66 (m, 2 H) 1.34-1.27 (m, 24 H), 0.93-0.89 (t, *J* = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$): δ 163.(d, *J* = 244 Hz), 155.5, 154.2, 140.5, 132.9 (d, *J* = 8.4 Hz), 131.8, 130.5 (d, *J* = 8.3 Hz), 127.6, 124.1, 120.7, 120.4 (d, *J* = 2.9 Hz), 115.1 (d, *J* = 21.2 Hz), 111.7 (d, *J* = 21.2 Hz), 110.9, 102.3, 29.9, 29.8, 29.7, 29.6, 29.5, 29.4, 22.7, 14.2; ^{19}F NMR ($CDCl_3$): δ -112.6; MS (EI, 70 ev): *m/z* (%) = 225 (100), 422 (M^+, 77), 43 (40), 41 (27), 423 (25), 226 (17); Anal. Calcd for $C_{29}H_{39}FO$: C, 82.42; H, 9.30; F, 4.50; found C, 82.37; H, 9.38; F, 4.57.

3q: mp 53-54 °C; IR (KBr) 2917, 2848 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.11 (s, 1 H), 8.03-8.01 (d, *J* = 6.9 Hz, 1 H), 7.61-7.51 (m, 3 H), 7.38 (s, 1 H), 7.12-7.09 (m, 2 H), 2.78-2.74 (t, *J* = 7.6 Hz, 2 H), 1.72-1. 66 (m, 2 H) 1.34-1.27 (m, 24 H), 0.93-0.89 (t, *J* = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$): δ 155.5, 153.8, 140.7, 131.6, 129.4, 127.2(q J=315 Hz), 125.5, 124.7, 124.2, 121.5, 120.8, 110.9, 102.6, 101.6, 36.3, 32.0, 31.9, 29.8, 29.7, 29.6, 29.4, 29.3, 22.8, 14.2; ^{19}F NMR ($CDCl_3$): δ - 62.8; MS (EI, 70 ev): *m/z* (%) = 275 (100), 472 (M+,72), 43 (35), 473 (23), 41.05 (22); Anal. Calcd for $C_{29}H_{39}F_3O$: C, 76.24; H, 8.32; F, 12.06;found C, 76.32; H, 8.37; F, 12.00.

Typical Procedure for preparation of 2,3-Disubstituted Benzo[*b*]furans (13) from *o*-Alkynylcardanols (12) and Aryl Iodides (10):

A mixture of iodobenzene (45μl, 0.4, mmol), $Pd_2(dba)_3$ (3.1 mg, 0.01 mmol), bpy (3.2 mg, 0.02 mmol) and K_2CO_3 (110 mg, 0.8 mmol) in MeCN (0.6 mL) was stirred at 50°C under Ar for 1 h. Then, a solution of **12a** (70 mg, 0.2 mmol) in MeCN (0.4 mL) was added. The reaction mixture was stirred for further 5 h. After this time, it was diluted with ethyl acetate and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 35 g; *n*-hexane) to give 65mg of **13a** (70% yield): mp 60-62 °C; IR (KBr): 2919, 2849 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.69-7.67 (m, 2 H), 7.55-7.32 (m, 10 H), 7.12 (m, 1 H), 2.80-2.76 (t, *J* = 7.6, 2 H), 1.73-1.70 (m, 2 H) 1.37-1.30 (m, 24 H), 0.93-0.90 (t, *J* = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 154.5, 150.0, 140.5, 131.0, 129.8, 129.0, 126.5, 128.2, 128.1, 127.6, 127.0, 123.7, 119.6, 117.5, 110.7, 36.3, 32.0, 29.8, 29.7, 29.6,

29.5, 29.4, 22.8, 14.2; MS (EI, 70 ev): *m/z* (%) = 404 (M^+, 100), 207 (98), 43 (38), 405 (32), 41 (26), 406 (5); Anal. Calcd for $C_{35}H_{44}O$: C, 87.45; H, 9.23. Found C, 87.55; H, 9.27.

13b: mp 61-63 °C; IR (KBr): 2918, 2846 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.70-7.69 (d, *J* = 7.1, 2 H), 7.60-7.58 (d, *J* = 8.8, 1 H), 7.46-7.30 (m, 5 H), 7.12-7.10 (d, *J* = 7.8, 1 H), 7.05-7.03 (d, *J* = 8.5, 2 H), 6.72-6.70 (d, *J* = 8.8, 1 H), 3.92 (s, 3 H) 2.80-2.76 (t, *J* = 7.6, 2 H), 1.73-1.70 (m, 2 H) 1.37-1.30 (m, 24 H), 0.93-0.90 (t, *J* = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$): δ 158.5, 153.8, 149.2, 139.8, 137.7, 130.6, 130.4, 128.0 127.8, 127.5, 126.3, 124.7, 123.2, 119.1, 116.6, 115.9, 113.9, 110.2, 54.8, 35.7, 31.5, 29.2, 29.2, 29.1, 28.9, 28.8, 22.2, 13.6.

MS (EI, 70 ev): *m/z* (%) = 510 (M^+, 100), 43.05 (67), 511 (39), 313 (23), 512 (17); Anal. Calcd for $C_{36}H_{46}O_2$: C, 84.66; H, 9.08. Found C, 84.72; H, 9.04.

13c: mp 65-67 °C; IR (KBr) 2919, 2849, 1682 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.08-8.06 (d, *J* = 8.2, 2 H), 7.86-7.84 (d, *J* = 8.4, 2 H), 7.69-7.63 (m, 4 H),7.41-7.35 (m, 1 H), 7.34-7.13 (m, 2 H), 7.14-7.12 (d, *J* = 8.0, 1 H), 2.79-2.75 (t, *J* = 7.6, 2 H), 2.59 (s, 3 H) 1.71-1.67 (m, 2 H) 1.37-1.30 (m, 24 H), 0.92-0.89 (t, *J* = 6.5 Hz, 3 H); ^{13}C NMR (CDCl3): δ 197.6, 154.4, 150.6, 140.6, 138.3, 137.8, 136.2, 136.0, 130.3, 129.7, 129.6, 128.9, 128.5, 128.4, 127.1, 127.0, 124.0, 119.2, 116.3, 110.7, 101.0, 36.1, 31.8, 31.8, 29.6, 29.5, 29.4, 29.3, 29.2, 26.6, 26.4, 22.6, 14.0; MS (EI, 70 ev): *m/z* (%) = 207 (100), 522 (M^+, 90), 523.35 (76), 43 (56), 325 (29); Anal. Calcd for $C_{37}H_{47}O_2$: C, 85.01; H, 8.87. Found C, 85.10; H, 8.81.

13d: mp 64-66 °C; IR (KBr): 2917, 2848, 1673 cm^{-1};^1H NMR ($CDCl_3$): δ 7.92-7.90 (d, *J* = 8.3, 2 H), 7.77-7.75 (d, *J* = 8.3, 2 H), 7.52-7.27 (m, 7 H),7.13-7.10 (m, 1 H), 2.80-2.76 (t, *J* = 7.6, 2 H), 2.60 (s, 3 H) 1.73-1.70 (m, 2 H) 1.37-1.30 (m, 24 H), 0.92-0.89 (t, *J* = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$): δ 197.5, 154.7, 148.6, 141.4, 136.1, 135.4, 132.8, 129.8, 129.2, 128.5, 128.1, 128.0 126.6, 124.2, 120.0, 119.9, 110.8, 36.4, 32.0, 31.9, 29.8, 29.6, 29.5, 29.4, 26.6, 22.8, 14.2; MS (EI, 70 ev): *m/z* (%) = 522 (M^+, 100), 325 (57), 523 (41), 43 (40), 41 (16); Anal. Calcd for $C_{37}H_{46}O_2$: C, 85.01; H, 8.87; found C, 85.07; H, 8.83.

13e: Oil; IR (neat) 2922, 2850 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.32 (s, 1 H), 7.70 - 7.68 (d, *J* = 8.2, 1 H), 7.52-7.48 (m, 7 H), 7.14-7.13 (m, 1 H), 7.26 (s, 1 H), 7.12-7.10 (m, 1 H), 2.80-2.76 (t, *J* = 7.6, 2 H), 2.60 (s, 3 H), 1.73-1.70 (m, 2 H) 1.37-1.30 (m, 24 H), 0.92-0.89 (t, *J* = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$): δ 154.5, 149.5, 147.4, 141.4, 141.0, 133.3, 133.1, 132.9, 132.3, 130.4, 130.3, 130.1, 129.6, 129.3, 126.6, 128.2, 127.8, 126.5, 124.3, 122.5, 120.8, 120.7, 119.9, 119.2,

110.9, 110.9, 102.8, 36.3, 32.0, 31.9, 31.9, 29.8, 29.7, 29.6, 29.4, 29.3, 22.8, 20.4, 20.3, 14.2; MS (EI, 70 ev): *m/z* (%) = 539 (M^+, 100), 43 (78), 342 (53), 462 (47), 540 (36), 541 (6); Anal. Calcd for $C_{36}H_{45}NO_3$: C, 80.11; H, 8.40; N, 2.60. Found C, 80.20; H, 8.47; N, 2.64.

13f: Oil; IR (neat) 2921, 2849 cm^{-1}; ^1H NMR (CDCl3): δ 8.35 (s, 1 H), 7.71-7.69 (d, *J* = 7.9, 1 H), 7.58-7.56 (d, *J* = 8.8, 1 H), 7.43-7.38 (m, 2 H), 7.26-7.23 (m, 1 H), 7.12-7.04 (m, 3 H), 6.71-6.69 (d, *J* = 8.8, 1 H), 3.91 (s, 3 H), 2.80-2.76 (t, *J* = 7.6, 2 H), 2.60 (s, 3 H), 1.73-1.70 (m, 2 H) 1.37-1.30 (m, 24 H), 0.92-0.89 (t, *J* = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$): δ 158.5, 154.1, 149.1, 147.4, 141.1, 137.0, 136.1, 132.8, 132.4, 130.0, 129.2, 128.7, 126.6, 124.0, 122.2, 119.1, 117.6, 110.4, 55.0, 35.7, 31.4, 31.3, 29.2, 29.1, 29.0, 28.8, 28.7, 26.1, 22.2, 19.7, 13.6; MS (EI, 70 ev): *m/z* (%) = 569 (M^+, 100), 372 (M^+, 85), 43 (50), 570 (39), 571 (10), 572 (2); Anal. Calcd for $C_{37}H_{47}NO_3$: C, 78.00; H, 8.31; N, 2.46. Found C, 78.15; H, 8.38; N, 2.40.

13g: Oil;IR (neat) 2922, 2850, 1683 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.33 (s, 1 H), 8.11-8.09 (d, *J* = 8.2, 2 H), 7.65-7.61 (m, 3 H), 7.42-7.39 (m, 2 H), 7.26 (s, 1 H), 7.15-7.13 (d, *J* = 8.3, 1 H), 2.80-2.76 (t, *J* = 7.6, 2 H), 2.70 (s, 3 H), 2.62 (s, 3 H) 1.73-1.70 (m, 2 H), 1.37-1.30 (m, 24 H), 0.92-0.89 (t, *J* = 6.5 Hz, 3 H);^{13}C NMR ($CDCl_3$): δ 197.0, 154.1, 149.1, 147.4, 141.1, 137.0, 136.1, 132.8, 132.4, 130.0, 129.2, 128.7, 126.6, 124.0, 122.2, 119.1, 117.6, 110.4, 35.7, 31.4, 31.3, 29.2, 29.1, 29.0, 28.8, 28.7, 26.1, 22.2, 19.7, 13.6; MS (EI, 70 ev): *m/z* (%) = 581 (M^+), 43 (73), 462 (58), 384 (46), 582 (45), 583 (6); Anal. Calcd for $C_{38}H_{47}NO_4$: C, 78.45; H, 8.14; N, 2.41. Found C, 78.52; H, 8.10; N, 2.47.

13h: mp 77-78 °C; IR (neat): 2919, 2848, 1715 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.00-7.98 (d, *J* = 8.5, 2 H), 7.75-7.73 (d, *J* = 8.5, 2 H), 7.51-7.28 (m, 7 H),7.13-7.11(d, *J* = 8.1, 1 H), 3.93 (s, 3 H), 2.80-2.76 (t, *J* = 7.6, 2 H), 1.73-1.70 (m, 2 H) 1.37-1.30 (m, 24 H), 0.92-0.89 (t, *J* = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$): δ 166.7, 154.6, 148.7, 141.2, 135.1, 132.6, 129.7, 129.2, 129.1, 128.0, 127.9, 126.4, 124.1, 119.9, 119.6, 110.7, 52.1, 36.2, 31.9, 31.8, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 22.7, 14.1; MS (EI, 70 ev): *m/z* (%) = 538 (M^+, 100), 341 (60), 539 (41), 43 (33), 41 (15); Anal. Calcd for $C_{37}H_{46}O_3$: C, 82.49; H, 8.61. Found C, 82.55; H, 8.67.

13i :mp 72-73 °C; IR (KBr): 2919, 2848, 1715 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.00-7.98 (d, *J* = 8.5, 2 H), 7.75-7.73 (d, *J* = 8.5, 2 H), 7.70-7.69 (m, 2 H), 7.60-7.58 (d, *J* = 8.8, 1 H), 7.12-7.10 (d, *J* = 7.8, 1 H), 7.05-7.03 (d, *J* = 8.5, 2 H), 6.72-6.70 (d, *J* = 8.8, 1 H), 3.93 (s, 3 H), 3.90 (s, 3

H), 2.80-2.76 (t, *J* = 7.6, 2 H), 1.73-1.70 (m, 2 H) 1.37-1.30 (m, 24 H), 0.92-0.89 (t, *J* = 6.5 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ 166.7, 159.9, 154.6, 148.7, 141.2, 135.1, 132.6, 129.7, 129.1, 127.9, 126.4, 124.1, 119.9, 119.6, 110.7, 54.7, 52.1, 36.2, 31.9, 31.8, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 22.7, 14.1; MS (EI, 70 ev): *m/z* (%) = 568.37 (M^+, 100 %), 569.40 (60.72 %), 43.05 (32.57 %),41.00 (15.43 %); Anal. Calcd for $C_{38}H_{48}O_4$: C, 80.24; H, 8.51. Found C, 80.32; H, 8.53.

13j: mp 82-83 °C; IR (KBr): 2919, 2848, 1715,1681 cm^{-1};^{1}H NMR (CDCl3): δ 8.08-8.06 (d, *J* = 8.2, 2 H), 7.99-7.97 (d, *J* = 8.4, 2 H), 7.86-7.84 (d, *J* = 8.4, 2 H), 7.75-7.73 (d, *J* = 8.4, 2 H), 7.23-7.13 (m, 2 H), 7.14-7.12 (m, 1 H), 3.93 (s, 3 H), 2.80-2.76 (t, *J* = 7.6, 2 H), 2.59 (s, 3 H), 1.73-1.70 (m, 2 H) 1.37-1.30 (m, 24 H), 0.92-0.89 (t, *J* = 6.5 Hz, 3 H); ^{13}C NMR (CDCl3): δ 196.8, 166.7, 154.6, 148.7, 141.2, 135.9, 135.1, 132.6, 129.7, 129.2, 128.0, 127.9, 126.4, 124.1, 119.9, 119.6, 110.7, 52.1, 36.2, 31.9, 31.8, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 22.7, 14.1; MS (EI, 70 ev): *m/z* (%) = 580 (M^+, 100), 581.36 (72), 43.10 (41),41 (16); Anal. Calcd for $C_{39}H_{48}O_4$: C, 80.65; H, 8.33. Found C, 80.58; H, 8.30.

13k: Oil; IR (neat): 3414, 2924, 2852 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.57-7.29 (m, 11 H), 7.13-7.11 (d, *J* = 7.9 Hz, 1 H), 6.07-6.06 (m, 1 H), 5.60 (s, 1 H), 2.76-2.72 (t, *J* = 7.6, 2 H),2.58-2.56 (m, 1 H), 1.73-1.70 (m, 2 H), 1.59(s, 1 H), 1.35-1.28 (m, 24 H), 0.92-0.89 (t, *J* = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$): δ 154.9, 151.8, 141.1, 140.7, 131.9, 129.4, 129.1 128.6, 128.0, 127.8, 126.7, 126.0, 124.0, 120.0, 119.6, 111.2, 68.6, 36.2, 32.0, 31.9, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 22.6, 22.7, 14.2; MS (EI, 70 ev): *m/z* (%) = 510 (M^+, 100), 43 (96), 493 (68), 41.05 (45), 105.05 (43), 511 (39), 433 (34); Anal. Calcd for $C_{36}H_{46}O_2$: C, 84.66; H, 9.08. Found C, 84.59; H, 9.02.

13l: Oil IR (neat): 3361, 2923, 2850 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.65-7.63 (d, *J* = 8 Hz, 2 H), 7.55-7.35 (m, 8 H), 7.15-7.13 (d, *J* = 7.9, 1 H), 6.10-6.09 (m, 1 H), 5.60 (s, 1 H), 3.95 (s, 3 H), 2.76-2.72 (t, *J* = 7.6, 2 H),2.58-2.56 (m, 1 H), 1.73-1.70 (m, 2 H), 1.59(s, 1 H), 1.35-1.28 (m, 24 H), 0.92-0.89 (t, *J* = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$): δ 160.5 154.9, 151.8, 141.1, 140.7, 131.9, 129.4, 129.1, 128.6, 127.8, 126.7, 126.0, 124.0, 120.0, 119.6, 111.2, 68.6, 56.2, 36.2, 32.0, 31.9, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 22.6, 22.7, 14.2; MS (EI, 70 ev): *m/z* (%) = 207 (100), 73 (65), 281 (40), 524 (23), 540 (M^+, 16), 43 (14); Anal. Calcd for $C_{37}H_{48}O_3$: C, 82.18; H, 8.95. Found C, 82.22; H, 8.97.

13m: Oil; IR (neat): 3442, 2924, 2853, 1685 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.05-8.03 (d, *J* = 8.1, 2 H), 7.83-7.81 (d, *J* = 8.1, 2 H), 7.57-7.29 (m, 6 H), 7.15-7.13 (d, *J* = 7.9 Hz, 1 H), 6.11-6.10 (m, 1 H), 5.60 (s, 1 H), 2.76-2.72 (t, *J* = 7.6, 2 H), 2.60 (s, 3 H), 2.58-2.56 (m, 1 H), 1.73-1.70 (m, 2H), 1.59 (s, 1 H), 1.35-1.28 (m, 24 H), 0.92-0.89 (t, *J* = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$): δ 197.0, 154.9, 151.8, 141.1, 140.7, 135.9, 131.9, 129.4, 129.1 128.6, 127.8, 126.7, 126.0, 124.0, 120.0, 119.6, 111.2, 68.6, 36.2, 32.0, 31.9, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2 22.6, 22.7, 14.2; MS (EI, 70 ev): *m/z* (%) = 73 (100), 552 (M^+, 76), 355 (58), 553 (15), 43 (12); Anal. Calcd for $C_{37}H_{48}O_3$: C, 82.56; H, 8.75. Found C, 82.52; H, 8.72.

4: mp 49 -50 °C.;IR (KBr) 2918, 2849, 1638 cm^{-1}; ^1H NMR (CDCl3): δ 12.3 (s, 1 H), 7.64-7.62 (d, *J* = 7.9 Hz, 1 H), 7.06-7.04 (dd, *J* = 7.9, *J* = 1.3 Hz, 1 H), 6.54 (s, 1 H), 2.73-2.72 (t, *J* = 7.6, 2 H), 1.66-1.61 (m, 8 H), 1.33-1.27 (m, 24 H), 0.91-0.88 (t, *J* = 6.5, 3 H);^{13}C NMR ($CDCl_3$): δ 203.9, 162.6, 153.1, 130.7, 119.6, 117.8, 36.3, 32.0, 30.7, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 26.5, 22.8, 14.2; MS (EI, 70 ev): *m/z* (%) = 43 (100), 150 (67), 346 (35), 41 (31); Anal. Calcd for $C_{23}H_{38}O_2$: C, 79.71; H, 11.05. Found C, 79.65; H, 11.09.

5: mp 62-63 °C;IR (KBr): 2918, 2848 cm^{-1};^1H NMR ($CDCl_3$): δ 7.78-7.76 (d, *J* = 8.9 Hz, 1 H), 6.82 -6.80 (d, *J* = 7.9 Hz, 1 H), 6.74 (s, 1 H), 2.70 (s, 2 H), 2.60-2.57 (t, *J* = 7.6, 2 H), 1.73-1.70 (m, 2 H) 1.46 (s, 6H), 1.37-1.30 (m, 24 H), 0.90-0.87 (t, *J* = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$): δ 192.3, 160.1, 152.7, 126.5, 121.5, 118.2, 117.7, 79.1, 48.9, 36.3, 32.0, 30.8, 29.6, 29.5, 29.4, 29.3, 26.8, 22.8, 14.2; MS (EI, 70 ev): *m/z* (%) = 371.25 (100), 43 (37), 372 (28), 386 (M^+, 10); Anal. Calcd for $C_{26}H_{42}O_2$: C, 80.77; H, 10.95. Found C, 80.85; H, 10.99.

8: mp 84-85°C;IR (KBr): 3310, 2920, 2849, 1652 cm^{-1}; ^1H NMR ($CDCl_3$): δ 12.5 (s, 1 H), 7.77-7.75 (d, *J* = 8.2 Hz, 1 H), 6.77 (s, 1 H), 6.73-6.70 (m, 1 H), 5.33 (s, 1 H), 3.53 (s, 3 H), 2.60-2.57 (t, *J* = 7.6, 2 H), 2.30-2.27 (m, 2 H), 1.91 (s, 2 H), 1.59-1.45 (m, 10 H), 1.37-1.30 (m, 24 H), 0.89-0.87 (t, *J* = 6.5 Hz, 3 H);^{13}C NMR ($CDCl_3$): δ 205.1, 170.4, 162.8, 153.1, 130.8, 119.6, 118.6, 117.7, 55.5, 36.2, 35.3, 32.0, 30.6, 29.8, 29.7, 29.6, 29.5,29.4, 29.3, 25.5, 24.5, 22.7, 21.7, 14.2; Anal. Calcd for $C_{31}H_{51}O_3$: C, 76.65; H, 10.58; N, 2.88. Found C, 76.58; H, 10.51; N, 2.81.

Appendix I. EXPERIMENTAL SECTION

Chapter 7-Experimental Section

Typical procedure for synthesis of **4a** from **3a** and phenil boronic acid**:** To a stirred solution of 3a (100mg,0.20mmol), $Pd_2(dba)_3$ (3.6mg, 0.004mmol), S-phos(3.2mg, 0.008mmol) and K_3PO_4 (127.1mg, 0.6 mmol), in 1.4ml of degassed toluene under Ar finally was added **phenilboronic acid** (36.4mg,0.30mmol), at 100°C, the reaction was monitored by TLC, after 5 h the mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over Na_2SO_4 concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 35 g; n-hexane/ Ethyl acetate = 50:50) to give 104 mg of **4a :** m.p.: 120-122°C; IR (KBr) 3497, 2998, 2935, 2837 cm^{-1}; ^{1}H NMR (CDCl3) δ 7.41-7.21 (m, 5H), 6.87-6.80 (m, 3H), 6.26 (s, 1H), 4.73-4.71 (d, J = 7.4 Hz, 1H), 4.15-3.98 (m, 1H), 3.90 (s, 3H), 3.88 (s, 3H) 3.86 (s, 3H), 3.84 (s, 3H),3.09-2.67 (m, 2H); ^{13}C NMR (CDCl3) δ 157.7, 156.7, 152.2, 149.2, 148.9, 134.0, 131.3, 130.9, 127.5, 126.4, 118.9, 111.8, 111.1, 109.5, 102.0, 88.9, 81.0, 68.3, 60.5, 56.2, 56.0, 55.8, 55.6, 31.6, 27.4; Anal. Calcd for $C_{25}H_{26}O_6$: C, 71.07; H, 6.20; found C, 71.15; H, 6.25.

4b : m.p.: 151 °C; IR (KBr) 3546, 3006, 2939, 2839cm^{-1}; ^{1}H NMR (CDCl3) δ 7.44-7.42 (m, 2H), 7.38-7.34 (m, 2H), 7.27-7.24 (m, 1H), 6.85-6.78 (m, 3H), 6.26 (s, 1H), 4.97 (s, 1H), 4.42 (m, 1H), 3.90 (s, 3H), 3.85 (s, 3H) 3.75 (s, 3H), 3.70 (s, 3H), 3.04-2.96 (m, 2H); ^{13}C NMR (CDCl3) δ 158.2, 156.6, 152.1, 149.0, 148.3, 134.2, 131.4, 130.7, 127.6, 126.4, 117.4, 112.0, 111.2, 109.4, 100.9, 89.1, 79.0, 66.1, 65.8, 56.2, 56.0, 55.8, 55.6, 31.6, 28.1; Anal. Calcd for $C_{25}H_{26}O_6$: C, 71.07; H, 6.20; found C, 71.11; H, 6.27.

4c: m.p.: 152-154°C; IR (KBr) 3526, 2992, 2939, 2837cm^{-1}; ^{1}H NMR (CDCl3) δ 7.31-7.29 (d, J= 8.0 Hz, 2H), 7.16-7.14 (d, J = 8.0 Hz, 2H), 6.91-6.82 (m, 4H), 6.26 (s, 1H), 4.69-4.67 (d, J= 7.4 Hz, 1H), 4.44 (m, 1H), 3.91 (s, 3H), 3.83 (s, 3H) 3.78 (s, 3H), 3.09-3.03 (m, 1H),3.08-3.04 (m, 1H), 2.74-2.68 (m, 1H), 2.37 (s, 3H); ^{13}C NMR (CDCl3) δ 157.5, 156.7, 152.2, 149.1, 148.8, 135.9, 131.1, 131.0, 130.9, 128.3, 119.0, 111.0, 109.4, 101.8, 88.8, 80.9, 68.2, 56.2, 56.0, 55.8, 55.6, 31.6, 27.3, 21.3; Anal. Calcd for $C_{26}H_{28}O_6$: C, 71.07; H, 6.20; found C, 71.10; H, 6.23.

4d: m.p.: 148-151°C; IR (KBr) 3528, 2990, 2941, 2837cm^{-1}; ^{1}H NMR (CDCl3) δ 7.36-7.34 (d,J = 8.0 Hz, 2H), 7.21-7.19 (d,J = 8.0 Hz, 2H), 6.88-6.85 (m, 3H), 6.28 (s, 1H), 5.00 (s,1H) 4.44

(m, 1H), 3.92 (s, 3H), 3.88 (s, 3H) 3.78 (s, 3H), 3.75 (s, 3H),3.11-2.95 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (CDCl3) δ 157.8, 156.5, 152.0, 148.9, 148.1, 135.6, 131.0, 130.9,130.6, 128.2, 117.2, 111.7, 111.0, 109.3, 100.6, 88.8, 65.6, 56.0, 55.8, 55.5, 55.4, 31.5, 27.9, 21.2; Anal. Calcd for $C_{26}H_{28}O_6$: C, 71.07; H, 6.20; found C, 71.15; H, 6.25.

4e : m.p.: 110-112°C; IR (KBr) 3529, 2990, 2939, 2838 cm^{-1}; ^{1}H NMR (CDCl3) δ 7.22-7.13 (m, 2H), 6.97-6.82 (m, 2H), 6.25 (s, 1H), 4.73-4.71 (d, J = 7.4 Hz, 1H), 4.15-3.98 (m, 1H), 3.90 (s, 3H), 3.88 (s, 3H) 3.86 (s, 3H), 3.84 (s, 3H),3.09-3.04 (m, 1H), 3.73-3.67 (m, 1H); ^{13}C NMR (CDCl3) δ 160.2 (d, J = 243.9 Hz), 157.7, 156.6, 152.2, 149.0 (d, J = 18.2 Hz), 134.3, 130.8, 130.1, 129.4, 123.6(d, J = 17.2 Hz), 119.0, 114.2(d, J = 22.2 Hz), 111.1, 109.5, 102.0, 88.9, 81.0, 68.3, 56.2, 56.0, 55.8, 55.6, 31.6, 27.4,22.7; ^{19}F NMR (CDCl3) δ = - 120.8; Anal. Calcd for $C_{26}H_{27}O_6F$: C, 68.71; H, 5.99; found C, 68.78; H, 5.95.

4f : m.p.: 99-101°C; IR (KBr) 3529, 2990, 2935, 2833 cm^{-1}; ^{1}H NMR (CDCl3) δ 7.31-7.21 (m, 2H), 7.02-7.97 (m, 1H), 6.90-6.84 (m, 3H), 6.19 (s, 1H), 4.98 (s,1H), 4.44 (m, 1H), 3.92 (s, 3H), 3.88 (s, 3H) 3.78 (s, 3H), 3.75 (s, 3H), 3.12-2.96 (m, 2H), 2.30(s, 3H); ^{13}C NMR (CDCl3) δ 160.2 (d, J = 243.5 Hz), 158.2, 156.6, 152.2, 148.7 (d, J = 18.3 Hz), 134.3, 130.6, 130.2, 129.7, 123.7 (d, J = 17.1 Hz), 117.6, 114.1(d, J = 22.2 Hz), 111.1, 109.5, 100.9, 88.9, 77.7, 65.8, 56.2, 56.0, 55.8, 55.6, 31.6, 28.0, 22.7; ^{19}F NMR (CDCl3) δ = - 121.0; Anal. Calcd for $C_{26}H_{27}O_6F$; C, 68.71; H, 5.99; found C, 68.75; H, 5.94.

4g: m.p.: 155-157°C; IR (KBr) 3562, 3006, 2932, 2836 cm^{-1}; ^{1}H NMR (CDCl3) δ 7.28-7.14 (m, 4H), 6.83-6.78 (m, 3H), 6.26 (s, 1H), 4.73-4.72 (m, 1H), 3.99-3.97 (m, 1H), 3.95 (s, 3H), 3.92 (s, 3H) 3.80 (s, 3H), 3.75 (s, 3H), 3.08-3.03 (m, 1H),2.75-2.68 (m, 1H), 2.13 (s, 3H); ^{13}C NMR (CDCl3) δ 157.7, 156.7, 152.2, 149.2, 148.9, 137.4, 134.1, 131.3, 130.9, 129.2, 126.9, 125.2, 119.1, 111.2, 110.9, 109.4, 102.7, 88.6, 81.0, 68.4, 56.1, 56.0, 55.8, 55.5, 27.4, 20.1; Anal. Calcd for $C_{26}H_{28}O_6$: C, 71.07; H, 6.20; found C, 71.15; H, 6.25.

4h: m.p.: 164-166°C; IR (KBr) 3496, 3007, 2938, 2837cm^{-1}; ^{1}H NMR (CDCl3) δ 7.30-7.21 (m, 3H), 6.85-6.81 (m, 3H), 6.73 (m, 1H), 6.28 (s, 1H), 4.97 (s,1H) 4.44 (m, 1H), 3.95 (s, 3H), 3.87 (s, 3H) 3.77 (s, 3H), 3.67 (s, 3H),3.11-2.95 (m, 2H), 2.13 (s, 3H); ^{13}C NMR (CDCl3) δ 158.2, 156.6, 152.1, 149.0, 148.3, 134.2, 131.4, 130.7, 127.6, 126.4, 117.4, 112.0, 111.2, 109.4, 100.9, 89.1, 79.0, 66.1, 65.8, 56.2, 56.0, 55.8, 55.6, 31.6, 28.1, 20.1 Anal. Calcd for $C_{26}H_{28}O_6$: C, 71.07; H, 6.20; found C, 71.15; H, 6.25.

4i: m.p.: 148-150°C; 3465, 2990, 2933, 2836cm $^{-1}$; ^{1}H NMR (CDCl3) δ 7.60-7.56 (m, 3H), 7.55-7.54 (m, 1H), 7.49-7.47(m, 2H), 7.43-7.39 (m, 2H), 7.33-7.29 (m, 1H), 6.90-6.87 (m, 2H), 6.83-6.80 (m, 1H), 6.27 (s, 1H), 4.75-4.73 (d, J = 7.5 Hz, 1H), 4.02-4.00 (m, 1H), 3.90 (s, 3H), 3.88 (s, 3H) 3.85 (s, 3H), 3.80 (s, 3H), 3.10-3.05 (m, 1H), 2.74-2.68 (m, 1H); ^{13}C NMR (CDCl3) δ 157.8, 156.7, 152.2, 149.9,148.8, 141.3,133.0, 131.7, 130.8, 128.7, 127.1, 127.0, 126.3, 119.0, 111.0, 109.6, 102.0, 88.8, 81.1, 68.2, 56.2, 56.0, 55.8, 55.6, 31.6, 27.3; Anal. Calcd for $C_{31}H_{30}O_6$: C, 74.68; H, 6.07; found C, 74.75; H, 6.00.

4j: m.p.: 188-190°C; 3544, 2060, 3029, 2931 cm $^{-1}$; ^{1}H NMR (CDCl3) δ 7.68-7.64 (m, 4H), 7.58-7.55 (m, 2H), 7.51-7.45(m, 2H), 7.37-7.31 (m, 1H), 6.90-6.84 (m, 3H), 6.30 (s, 1H), 5.00 (s,1H) 4.44 (m, 1H), 3.92 (s, 3H), 3.88 (s, 3H) 3.78 (s, 3H), 3.75 (s, 3H), 3.12-2.96 (m, 2H);^{13}C NMR (CDCl3) δ 157.7, 156.7, 152.1, 149.9, 148.8, 141.3,133.0, 131.7, 130.8, 128.7, 127.1, 127.0, 126.3, 119.0, 111.0, 109.6, 102.0, 88.8, 81.1, 68.2, 56.2, 56.0, 55.8, 55.4, 31.6, 27.9; Anal. Calcd for $C_{31}H_{30}O_6$: C, 74.68; H, 6.07; found C, 74.73; H, 6.05.

Appendix II – PAPERS

Gianfranco Battistuzzi, Sandro Cacchi, Ilse De Salve, Giancarlo Fabrizi, Luca M. Parisi
Synthesis of Coumarins in a Molten n-Bu4NOAc/n-Bu4NBr Mixture through a Domino Heck Reaction/Cyclization Process. *Advanced Synthesis & Catalysis (2005), 347(2-3), 308-312.*

Bernini Roberta, Sandro Cacchi, Ilse De Salve, Giancarlo Fabrizi.
The Heck Reaction of β-Aryl acrilammides. An approach to 4-Aryl-2-Quinolones. *Synlett.* **In press.**

Gianfranco Battistuzzi, Bernini Roberta, Sandro Cacchi, Ilse De Salve, Giancarlo Fabrizi.
2-Quinolones through a Pseudo-Domino Heck/Buchwald_Hartwig CYclization Process in a molten n-Bu4NOAc/n-Bu4NBr Mixture. *Advanced Synthesis & Catalysis.* **In press.**

Bernini Roberta, Sandro Cacchi, Ilse De Salve, Giancarlo Fabrizi.
Palladium-Catalyzed Synthesis of Lipophilic Benzo[b]furans from Cardanol. *Synthesis.* **In press**

Appendix III – COMMUNICATIONS

POSTER COMMUNICATION

7° Congresso nazionale del Consorzio I.N.C.A. - Venezia 2-3 Settembre 2004 – Università Ca' Foscari - Auditorium S. Margherita

Roberta Bernini, Sandro Cacchi, Ilse M.L. De Salve, Giancarlo Fabrizi, Enrico Mincione:

" *Molten Salt Mixtures as Reusable Reaction Media For The Palladium-Catalyzed Heck Reaction".*

7° Summer School on Green Chemistry - Venezia 5-11 Settembre 2004.

Roberta Bernini, Sandro Cacchi, Ilse M.L. De Salve, Giancarlo Fabrizi, Enrico Mincione:

" *Molten Salt Mixtures as Reusable Reaction Media For The Palladium-Catalyzed Heck Reaction".*

XXX Scuola "A. Corbella" di Chimica Organica – Gargnano 13-17 Giugno 2005.

Bernini Roberta, Ilse M. L. De Salve, Fabrizi Giancarlo, Cavani Fabrizio:

"Phenols derivatives oxidation using the O_2/POM catalytic system".

Stereocat 2005 COST meeting D24, Barcellona 15-18 Settembre 2005.

Sandro Cacchi, Ilse M. L. De Salve, Giancarlo Fabrizi:

"2-Quinolones through a Pseudo-Domino Heck/Buchwald_Hartwig CYclization Process in a molten n-Bu4NOAc/n-Bu4NBr Mixture".

8° Congresso nazionale del consorzio I.N.C.A. - Bologna 23-24 Marzo 2005 – Università di Bologna-Facoltà di Ingegneria.

Sandro Cacchi, Ilse M. L. De Salve, Giancarlo Fabrizi:

"2-Quinolones through a Pseudo-Domino Heck/Buchwald_Hartwig CYclization Process in a molten n-Bu4NOAc/n-Bu4NBr Mixture"

Appendix III – COMMUNICATIONS

ORAL COMMUNICATION

COST meeting , 5-7 OCTOBER-2006, Rome

Sandro Cacchi, Ilse M. L. De Salve, Giancarlo Fabrizi:

Palladium-Catalyzed Synthesis of Lipophilic Benzo[b]furans from Cardanol. Oral communication

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